A. INGREDIENT NAME:

GUAIACOL

B. Chemical Name:

Guajacol, Guaiacol, Guaicoo, Guajakol (CZECH), O-Hydroxyanisole,2-Hydroxyanisole, 1-Hydroxy-2-Methoxybenzene, O-Methoxyphenol, 2-Methoxyphenol, Methylcatechol, Pyroguaiac Acid

C. Common Name:

Austral: Waterbury's Compound, Belg: Baume Dalet, Canada: Cre-Rectal, etc. Various names from different countries. Please see file.

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

	(Specifications)	*(Results)*
Assay:	99.5% min.	99.7%

E. Information about how the ingredient is supplied:

White or slightly yellow crystal mass or colorless to yellowish, very refractive liquid, characteristic odor, darkens to exposure to air and light.

F. Information about recognition of the substance in foreign pharmacopeias:

Arg., Braz., Chil., Fr., It., Mex., Port., Roum,., Span., and Swiss.

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

H. Information about dosage forms used:

Expectorant

I. Information about strength:

0.3-0.6ml

J. Information about route of administration:

Orally

K. Stability data:

Boiling Point: 205C
Melting Point: 27C to 29C

L. Formulations:

M. Miscellaneous Information:

CERTIFICATE OF ANALYSIS

30-1709
50703

PRODUCT: GUAIACOL LIQUID
RELEASE #: N

LOT # :X49993D28

GRADE:PURIFIED
CODE:R9128201

	SPECIFICATIONS	RESULT
1. Description	Colorless liquid , characteristic odor	Conforms
2. Solidification point	27.5 deg C min.	28.0 deg C
3. Assay	99.5% min.	99.7% D

ATTENTION: TONY HATCHETT

Date :06/06/97

Prepared by : A.M. Scullion/MS

9257

Approved by :

6/97

Our Order # 234202 Your PO # 52409

QUALITY CONTROL REPORT

CHEMICAL NAME.: GUAIACOL PURIFIED (LIQUID) _____

MANUFACTURE LOT NO.: X49993D28

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP__/BP__/MERCK__/NF__/MART.__/CO.SPECS.__.

1) DESCRIPTION.:
WHITE OR SLIGHTLY YELLOW CRYSTAL MASS OR COLORLESS TO YELLOWISH, VERY REFRACTIVE LIQUID; CHARACTERISTIC ODOR; DARKENS ON EXPOSURE TO AIR AND LIGHT.

2) SOLUBILITY.:
1gm DISSOLVES IN 60-70ml WATER, 1ml GLYCEROL; MISCIBLE WITH ALCOHOL, CHLOROFORM, ETHER, OILS, GLACIAL ACETIC ACID; SOLUBLE IN NAOH SOLUTION; WITH MODERATELY CONC KOH, IT FORMS A SPARINGLY SOLUBLE COMPOUND.

3) MELTING POINT.:

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:
A) COMPLIES IR SPECTRUM AS PER COMPANY SPECS.

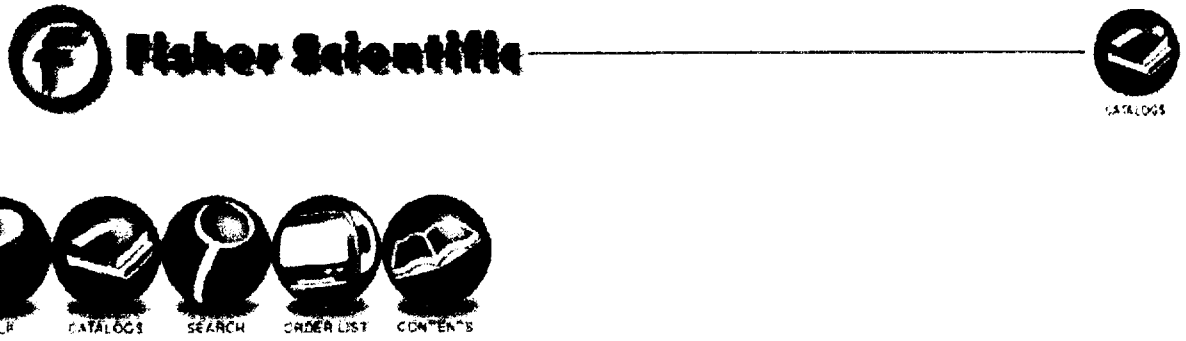
PASSES.: _____ **FAILS.:** _____

COMMENTS.:

ANALYST SIGNATURE.: _____ **DATE.:** _____

PREPACK TEST.: _____ **DATE.:** _____ **INITIAL.:** _____

RETEST.: _____ **DATE.:** _____ **INITIAL.:** _____



Use your web browser's "Back" key to return to previous topic.

MATERIAL SAFETY DATA SHEET

Guaiacol, 99+%
06742

**** SECTION 1 - CHEMICAL PRODUCT AND COMPANY IDENTIFICATION ****

MSDS Name: Guaiacol, 99+%

2-Methoxyphenol
Company Identification: Acros Organics N.V.
One Reagent Lane
Fairlawn, NJ 07410
For information in North America, call: 800-ACROS-01
For emergencies in the US, call CHEMTREC: 800-424-9300
For emergencies in the US, call CHEMTREC: 800-424-9300

**** SECTION 2 - COMPOSITION, INFORMATION ON INGREDIENTS ****

CAS#	Chemical Name	%	EINECS#
90-05-1	GUAIACOL	99+	201-964-7

Hazard Symbols: XN
Risk Phrases: 22 36/38

**** SECTION 3 - HAZARDS IDENTIFICATION ****

EMERGENCY OVERVIEW

Appearance: clear slightly yellow. Flash Point: 82 deg C.
Light sensitive. Air sensitive.
Target Organs: Central nervous system, eyes, skin.

Potential Health Effects

Eye:
Causes eye irritation. Causes redness and pain.

Skin:
Causes severe skin irritation. May be absorbed through the skin.
Causes redness and pain.

Ingestion:
Harmful if swallowed. May cause gastrointestinal irritation with nausea, vomiting and diarrhea.

Inhalation:
May cause respiratory tract irritation.

Chronic:
Not available.

**** SECTION 4 - FIRST AID MEASURES ****

Eyes:
Immediately flush eyes with plenty of water for at least 15 minutes, occasionally lifting the upper and lower lids. Get medical aid.
Skin:
Get medical aid. Flush skin with plenty of soap and water for at least 15 minutes while removing contaminated clothing and shoes.
Ingestion:
Get medical aid. Wash mouth out with water.
Inhalation:
Remove from exposure to fresh air immediately. If not breathing, give artificial respiration. If breathing is difficult, give oxygen.
Notes to Physician:
Treat symptomatically and supportively.

**** SECTION 5 - FIRE FIGHTING MEASURES ****

General Information:
As in any fire, wear a self-contained breathing apparatus in pressure-demand, MSHA/NIOSH (approved or equivalent), and full protective gear. Combustible Liquid.
Extinguishing Media:
In case of fire use water spray, dry chemical, carbon dioxide, or chemical foam.
Autoignition Temperature: 385 deg C (725.00 deg F)
Flash Point: 82 deg C (179.60 deg F)
NFPA Rating: Not published.
Explosion Limits, Lower: Not available.
Upper: Not available.

**** SECTION 6 - ACCIDENTAL RELEASE MEASURES ****

General Information: Use proper personal protective equipment as indicated in Section 8.
Spills/Leaks:
Absorb spill with inert material, (e.g., dry sand or earth), then place into a chemical waste container. Remove all sources of ignition. Use a spark-proof tool.

**** SECTION 7 - HANDLING and STORAGE ****

Handling:
Avoid breathing dust, vapor, mist, or gas. Avoid contact with skin and eyes. Use only in a chemical fume hood.
Storage:
Keep away from sources of ignition. Store in a cool, dry place. Do not store in direct sunlight. Store in a tightly closed container.

**** SECTION 8 - EXPOSURE CONTROLS, PERSONAL PROTECTION ****

Engineering Controls:
Use adequate ventilation to keep airborne concentrations low.

Exposure Limits

Chemical Name	ACGIH	NIOSH	OSHA - Final PELs
GUAIACOL	none listed	none listed	none listed

OSHA Vacated PELs:
GUAIACOL:
No OSHA Vacated PELs are listed for this chemical.

Personal Protective Equipment

Eyes:
Wear appropriate protective eyeglasses or chemical safety goggles as described by OSHA's eye and face protection regulations in 29 CFR 1910.133.

Skin:
Wear appropriate protective gloves to prevent skin exposure.

Clothing:
Wear appropriate protective clothing to prevent skin exposure.

Respirators:
Follow the OSHA respirator regulations found in 29CFR 1910.134. Always use a NIOSH-approved respirator when necessary.

**** SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES ****

Physical State:	Liquid
Appearance:	clear slightly yellow
Odor:	Aromatic odor
pH:	Not available.
Vapor Pressure:	7 hPa @ 79 deg C
Vapor Density:	4.3
Evaporation Rate:	Not available.
Viscosity:	Not available.
Boiling Point:	205 deg C @ 760.00mm Hg
Freezing/Melting Point:	27 - 29 deg C
Decomposition Temperature:	Not available.
Solubility:	1.7 G/100ML WATER (15°C)
Specific Gravity/Density:	1.1290g/cm3
Molecular Formula:	C7H8O2
Molecular Weight:	124.14

**** SECTION 10 - STABILITY AND REACTIVITY ****

Chemical Stability:
Stable under normal temperatures and pressures.
Conditions to Avoid:
Incompatible materials, light, exposure to air.
Incompatibilities with Other Materials:
Strong oxidizing agents - strong bases - acid chlorides - acid anhydrides.
Hazardous Decomposition Products:
Carbon monoxide, carbon dioxide.
Hazardous Polymerization: Will not occur.

**** SECTION 11 - TOXICOLOGICAL INFORMATION ****

RTECS#:
CAS# 90-05-1: SL7525000
LD50/LC50:
CAS# 90-05-1: Inhalation, mouse: LC50 =7570 mg/m3; Oral, mouse: LD50 = 621 mg/kg; Oral, rat: LD50 = 520 mg/kg; Skin, rabbit: LD50 = 4600 mg/kg.
Carcinogenicity:
GUAIACOL -
Not listed by ACGIH, IARC, NIOSH, NTP, or OSHA.

**** SECTION 12 - ECOLOGICAL INFORMATION ****

Ecotoxicity:
EC 50 (24 hr) Daphnia magna: 63 mg/l
Environmental Fate:
Guaiacol is biodegradable.
Physical/Chemical:
Not available.
Other:
Not available.

**** SECTION 13 - DISPOSAL CONSIDERATIONS ****

Dispose of in a manner consistent with federal, state, and local regulations.
RCRA D-Series Maximum Concentration of Contaminants: Not listed.
RCRA D-Series Chronic Toxicity Reference Levels: Not listed.
RCRA F-Series: Not listed.
RCRA P-Series: Not listed.

RCRA U-Series: Not listed.
Not listed as a material banned from land disposal according to RCRA.

**** SECTION 14 - TRANSPORT INFORMATION ****

US DOT
No information available
IMO
Not regulated as a hazardous material.
IATA
Not regulated as a hazardous material.
RID/ADR
Not regulated as a hazardous material.
Canadian TDG
No information available.

**** SECTION 15 - REGULATORY INFORMATION ****

US FEDERAL
TSCA
CAS# 90-05-1 is listed on the TSCA inventory.
Health & Safety Reporting List
None of the chemicals are on the Health & Safety Reporting List.
Chemical Test Rules
None of the chemicals in this product are under a Chemical Test Rule.
Section 12b
None of the chemicals are listed under TSCA Section 12b.
TSCA Significant New Use Rule
None of the chemicals in this material have a SNUR under TSCA.
SARA
Section 302 (RQ)
None of the chemicals in this material have an RQ.
Section 302 (TPQ)
None of the chemicals in this product have a TPQ.
SARA Codes
CAS # 90-05-1: acute, flammable.
Section 313
No chemicals are reportable under Section 313.
Clean Air Act:
This material does not contain any hazardous air pollutants.
This material does not contain any Class 1 Ozone depletors.
This material does not contain any Class 2 Ozone depletors.
Clean Water Act:
None of the chemicals in this product are listed as Hazardous Substances under the CWA.
None of the chemicals in this product are listed as Priority Pollutants under the CWA.
None of the chemicals in this product are listed as Toxic Pollutants under the CWA.
OSHA:
None of the chemicals in this product are considered highly hazardous by OSHA.
STATE
Not present on state lists from CA, PA, MN, MA, FL, or NJ.
California No Significant Risk Level:
None of the chemicals in this product are listed.
European/International Regulations
European Labeling in Accordance with EC Directives
Hazard Symbols: XN
Risk Phrases:
R 22 Harmful if swallowed.
R 36/38 Irritating to eyes and skin.
Safety Phrases:
S 26 In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.
WGK (Water Danger/Protection)
CAS# 90-05-1: 1
Canada
CAS# 90-05-1 is listed on Canada's DSL/NDSL List.
WHMIS: Not available.
CAS# 90-05-1 is listed on Canada's Ingredient Disclosure List.
Exposure Limits

**** SECTION 16 - ADDITIONAL INFORMATION ****

MSDS Creation Date: 11/03/1991 Revision #2 Date: 9/02/1997

The information above is believed to be accurate and represents the best information currently available to us. However, we make no warranty of merchantability or any other warranty, express or implied, with respect to such information, and we assume no liability resulting from its use. Users should make their own investigations to determine the suitability of the information for their particular purposes. In no way shall Fisher be liable for any claims, losses, or damages of any third party or for lost profits or any special, indirect, incidental, consequential or exemplary damages, howsoever arising, even if Fisher has been advised of the possibility of such damages.

Back to product information.

BP-1988

A colourless, corrosive liquid with a pungent odour; weight per ml, about 1.22 g.

Formic Acid Solution, Non-aqueous A 5% v/v solution of *anhydrous formic acid* in *chloroform*.
Non-aqueous Formic Acid Solution should be freshly prepared; it is an extremely corrosive material.

D-Fructose Laevulose; $C_6H_{12}O_6$ = 180.2
General reagent grade of commerce.
A white, crystalline powder; melting point, about 103° with decomposition; $[\alpha]_D^{20}$, about −92° (10% w/v in water containing 0.05 ml of 5M ammonia).

L-Fucose 6-Deoxy-L-galactose; $C_6H_{12}O_5$ = 164.2
General reagent grade of commerce.
A white powder; melting point, about 140°; $[\alpha]_D^{20}$, about −76° (9% w/v in water measured after 24 hours).

Furfuraldehyde Furfural; furan-2-aldehyde; $C_5H_4O_2$ = 96.09
General reagent grade of commerce.
A colourless or pale brownish-yellow, oily liquid; boiling point, about 162°; weight per ml, about 1.16 g.

D-Galactose $C_6H_{12}O_6$ = 180.2
General reagent grade of commerce.
A white, crystalline powder; melting point, about 164°; $[\alpha]_D^{20}$, about +80° (10% w/v in water).

Gallic Acid 3,4,5-Trihydroxybenzoic acid; $C_7H_6O_5,H_2O$ = 188.1
General reagent grade of commerce.
Melting point, about 260°.

Gelatin Of the British Pharmacopœia.

Gelatin, Pancreatic Digest of
Microbiological reagent grade of commerce.

Gitoxin $C_{41}H_{64}O_{14}$ = 781.0
General reagent grade of commerce.
A white, crystalline powder; melting point, about 283°, with decomposition; $[\alpha]_D^{20}$, about +22° (0.5% w/v in a mixture of equal volumes of chloroform and methanol).
Complies with the following test.
HOMOGENEITY Carry out test A for Identification described under Digitalis Leaf applying to the chromatoplate a solution containing only the reagent being examined. The chromatogram shows only one spot.

D-Glucose Dextrose; $C_6H_{12}O_6$ = 180.2
Analytical reagent grade of commerce.
A white, crystalline or granular powder; $[\alpha]_D^{20}$, about +52.5° (10% w/v in water containing 0.2 ml of 5M ammonia).

D-Glucose Monohydrate $C_6H_{12}O_6,H_2O$ = 198.2
General reagent grade of commerce.
Colourless crystals or a white to cream, crystalline powder; $[\alpha]_D^{20}$, about +52.5° (10% w/v in water containing 0.2 ml of 5M ammonia).

Glycerol Propane-1,2,3-triol; $HOCH_2{\cdot}CHOH{\cdot}CH_2OH$ = 92.10
Analytical reagent grade of commerce.
A colourless viscous liquid; weight per ml, about 1.26 g.

Glycerol (85%) Glycerol containing 12.0 to 16.0% w/w of water; weight per ml, 1.22 to 1.24 g.

Glycerol Triacetate Triacetin; $C_9H_{14}O_6$ = 218.2
General reagent grade of commerce.
A colourless liquid; weight per ml, about 1.16 g.

Glycine Aminoacetic acid; $H_2NCH_2{\cdot}CO_2H$ = 75.1
Analytical reagent grade of commerce.

Glycollic Acid Hydroxyacetic acid; $HOCH_2{\cdot}CO_2H$ = 76.05
General reagent grade of commerce.
Slightly hygroscopic crystals; melting point, about 80°.

Glycyrrhetic Acid Glycyrrhetinic acid; a mixture of α- and β-isomers with the β-isomer predominating; $C_{30}H_{46}O_4$ = 470.7
General reagent grade of commerce.
A white to brownish-yellow powder; melting point, about 292°, with decomposition; $[\alpha]_D^{20}$, about +160° (1% w/v in chloroform).

β-Glycyrrhetinic Acid 3β-Hydroxy-11-oxo-18β,20β-olean-12-enoic acid; $C_{30}H_{46}O_4$ = 470.7
General reagent grade of commerce.
Melting point, about 293°; $[\alpha]_D^{20}$, about +170° (1% w/v in chloroform).

Glyoxal Bis(2-hydroxyanil) Bis(2-hydroxyphenylimino)-ethane; $C_{14}H_{12}N_2O_2$ = 240.3
General reagent grade of commerce.
Melting point, about 200°.

Glyoxal Sodium Bisulphite
$(HOCH{\cdot}SO_3Na)_2,H_2O$ = 284.2
General reagent grade of commerce.
A white or cream powder.

Gonadotrophin, Chorionic
General reagent grade of commerce.
A white or almost white, amorphous powder.

Gonadotrophin, Serum
General reagent grade of commerce.
A white or pale grey, amorphous powder.

Green S CI 44090; E142; lissamine green; acid brilliant green BS
Indicator grade of commerce.

Guaiacol *o*-Methoxyphenol; $CH_3O{\cdot}C_6H_4{\cdot}OH$ = 124.1
General reagent grade of commerce.
Colourless or pale yellow or pink crystals with an aromatic odour; melting point, about 28°.

Guaiacol Solution A 5% w/v solution of *guaiacol* in *ethanol (96%)*.
Guaiacol Solution should be protected from light.

Guaiacum Resin Resin obtained from the heartwood of *Guaiacum officinale* L. and *Guaiacum sanctum* L.
Reddish-brown or greenish-brown, glassy fragments.

Guaiacum Tincture Macerate in a stoppered flask 20 g of *guaiacum resin* with 100 g of *ethanol (80%)* for 24 hours, shaking occasionally, and filter.

Guaiazulene 1,4-Dimethyl-7-isopropylazulene; $C_{15}H_{18}$ = 198.3
General reagent grade of commerce.
Dark blue crystals or a blue liquid; melting point, about 29°.
Guaiazulene should be protected from light and air.

Guanine 2-Aminopurin-6-one; $C_5H_5N_5O$ = 151.1
General reagent grade of commerce.

Heavy Metals Masking Solution To 2.0 ml of 2M *ammonia* add, in the following order, 1.5 ml of a 5% w/v solution of *ammonium oxalate*, 15 ml of a 5% w/v solution of *potassium cyanide*, 45 ml of a 10% w/v solution of *sodium acetate*, 120 ml of a 50% w/v solution of *sodium thiosulphate*, 75 ml of a 10% w/v solution of *sodium acetate* and 35 ml of 1M *hydrochloric acid*.
Heavy Metals Masking Solution should be prepared immediately before use.

PREPARATIONS

Euphorbia Liquid Extract (*B.P.C.* 1949). Ext. Euphorb. Liq. 1 in 1: prepared by percolation with alcohol (45%). *Dose:* 0.12 to 0.3 ml.

Mist. Euphorb. Co. (*N.F.* 1939). Euphorbia liquid extract 0.6 ml, potassium iodide 450 mg, sodium bromide 450 mg, glyceryl trinitrate solution 0.06 ml, ethereal lobelia tincture 0.4 ml, water to 15 ml. *Dose:* 15 ml.

AMENDED FORMULA. Euphorbia liquid extract 0.5 ml, potassium iodide 450 mg, sodium bromide 450 mg, glyceryl trinitrate solution 0.05 ml, ethereal lobelia tincture 0.4 ml, water to 10 ml.—*Compendium of Past Formulae 1933 to 1966*, London, The National Pharmaceutical Union, 1969.

NOTE. **Euphorbium** (*B.P.C.* 1934, *Neth.P., Nord.P., Port.P., Span.P., Swiss P.*) is the dried latex from the stem of *Euphorbia resinifera*. It is emetic and powerfully purgative but it is not used internally on account of its violent action and its tendency to cause acute nephritis. The powder is violently sternutatory. Externally, it acts as a vesicant and was used for this purpose in veterinary medicine.

Garlic (*B.P.C.* 1949, *Span. P.*). Allium; Ail.

The fresh bulb of *Allium sativum* (Liliaceae). It has a very strong and disagreeable odour and a strongly pungent and persistent taste. It yields 0.1 to 0.3% of a volatile oil containing allyl propyl disulphide and diallyl disulphide. **Stored** in a cool dry place with free access of air it may be kept for about 6 months after harvesting.

Garlic has expectorant, diaphoretic, disinfectant, and diuretic properties, and the juice was formerly used alone or in a syrup in the treatment of pulmonary conditions. *Precautions:* administration of preparations of garlic to children is dangerous and fatalities have been recorded. *Dose:* 2 to 8 g.

The larvicidal principles of garlic active against the *Culex* mosquito were found to be diallyl di- and trisulphides. Natural and synthetic samples proved fatal at 5 ppm.—S. V. Amonkar and A. Banerji, *Science, Wash.*, 1971, *174*, 1343.

A report of allergic contact dermatitis to garlic.—E. Bleumink *et al.*, *Br. J. Derm.*, 1972, *87*, 6.

Garlic juice and the extracted essential oil prevented the hyperlipaemia and blood coagulation changes following fat ingestion in 5 healthy subjects.—A. Bordia and H. C. Bansal (letter), *Lancet*, ii/1973, 1491.

HYPERTENSION. In 5 consecutive cases of hypertension, garlic reduced the blood pressure to satisfactory levels.—V. Srinivasan (letter), *Lancet*, ii/1969, 800.

PREPARATIONS

Garlic Juice (*B.P.C.* 1949). Succus Allii. Bruise garlic 80 g and express the juice; mix the marc with water 20 ml and again express the liquid; repeat the operation until the volume of the mixed juice and washings amounts to 80 ml, and add alcohol (90%) 20 ml; allow to stand for 14 days, and decant or filter. *Dose:* 2 to 4 ml.

Garlic Syrup (*B.P.C.* 1949). Syr. Allii. Garlic juice 20 ml, sucrose 80 g, dilute acetic acid 20 ml, water 20 ml. *Dose:* 2 to 8 ml.

Grindelia (*B.P.C.* 1949). Grindelia Robusta; Gum Plant; Gumweed; Tar Weed.

Foreign Pharmacopoeias: In *Span.* In *Belg.* and *Braz.* which allow also the dried leaves and flowering tops of the marsh gumweed, *G. humilis*, and of the curly-cup gumweed, *G. squarrosa*. In *Fr.* and *Port.* which allow also *G. squarrosa*.

The dried leaves and flowering tops of the field gumweed, *Grindelia camporum* (Compositae) containing not less than 20% of alcohol (90%)-soluble extractive. **Store** in a cool dry place.

Grindelia has expectorant properties and has been stated to exert a spasmolytic effect. It has been used as a liquid extract in the treatment of asthma and bronchitis. Large doses sometimes cause renal irritation. Its nauseous taste may be masked with chloroform or glycerol.

PREPARATIONS

Grindelia Liquid Extract (*B.P.C.* 1949). Ext. Grindel. Liq. Grindelia 100 g is exhausted by percolation with alcohol (90%), the alcohol is removed by distillation, and the residue is dissolved in water 50 ml to which 10 g of sodium bicarbonate has previously been added; after effervescence has ceased, the solution is adjusted to 100 ml with alcohol (90%) and filtered. *Dose:* 0.6 to 1.2 ml.

Guaiacol (*B.P.C.* 1949). Gaïacol; Methyl Catechol.

Foreign Pharmacopoeias: In *Arg., Braz., Chil., Fr., It., Mex., Port., Roum., Span.*, and *Swiss*.

A colourless or almost colourless oily liquid or crystals with a penetrating aromatic odour and a caustic taste, obtained as a liquid by fractional distillation of wood-tar creosote or, usually as crystals, by synthesis. The main constituent is *o*-methoxyphenol, $CH_3O.C_6H_4.OH = 124.1$. Wt per ml (liquid) about 1.12 g; m.p. (crystals) about 28°. It tends to become yellowish on exposure to light.

Soluble 1 in 80 of water; miscible with alcohol, chloroform, ether, glacial acetic acid, and fixed and volatile oils; soluble 1 in 1 of glycerol but separates out on the addition of water. **Incompatible** with ferric salts. **Protect** from light.

Guaiacol has disinfectant properties similar to those of creosote. It has been used as an expectorant. *Toxic effects:* as for Phenol, p. 529. *Dose:* 0.3 to 0.6 ml.

Guaiacol Carbonate (*B.P.C.* 1949). Duotal. $(CH_3O.C_6H_4.O)_2.CO = 274.3$.

Foreign Pharmacopoeias: In *Chil., Port.*, and *Span.*

Guaiacol carbonate is the carbonic ester of guaiacol. It is a white, almost odourless, tasteless, crystalline powder. M.p. 83° to 88°.

Insoluble in water; soluble 1 in 70 of alcohol and 1 in 20 of ether; readily soluble in chloroform; slightly soluble in glycerol and fixed oils. It is decomposed by alcoholic potassium hydroxide solution and guaiacol separates from the solution on the addition of excess acid.

Guaiacol carbonate has the actions of guaiacol but is less irritant. It liberates guaiacol slowly and incompletely in the intestines, the larger part passing through the alimentary tract unchanged. *Dose:* 0.3 to 1 g.

Guaiphenesin (*B.P.C.*). Guaiacyl Glyceryl Ether; Guaiacol Glycerol Ether; Guaifenesin (*U.S.N.F.*); Glyceryl Guaiacolate; Glycerylguayacolum. 3-(*o*-Methoxyphenoxy)propane-1,2-diol. $C_{10}H_{14}O_4 = 198.2$.

Foreign Pharmacopoeias: In *Cz.* and *Roum.* Also in *U.S.N.F.*

Dose: 100 to 200 mg every 2 to 4 hours.

White odourless or almost odourless crystals or crystalline aggregates with a bitter taste. M.p. 80° to 82°.

Soluble 1 in 33 of water at 20°, 1 in 11 of alcohol and of chloroform, and 1 in 200 of ether; soluble 1 in 15 of glycerol with warming, 1 in 15 of propylene glycol, and 1 in 80 of sorbitol syrup. A 2% solution in water has a pH of 5 to 7 and is clear and colourless. Aqueous solutions are stable and may be **sterilised** by autoclaving. **Store** in airtight containers.

Toxic Effects and Precautions. Side-effects are rare with guaiphenesin. Gastro-intestinal discomfort and drowsiness have been reported.

A metabolite of guaiphenesin was found to produce an apparent increase in urinary 5-hydroxyindoleacetic acid, and guaiphenesin could thus interfere with the diagnosis of the carcinoid syndrome. Asthmatic patients being evaluated for the carcinoid syndrome should therefore discontinue any preparation containing guaiphenesin for 24 hours before the collection of urine specimens for the determination of 5-hydroxyindoleacetic acid. Acetanilide, mephenesin, and methocarbamol had been reported to cause similar false positive reactions, and hexamine mandelate and some phenothiazine derivatives to cause false negative reactions.—A. T. Pedersen *et al.*, *J. Am. med. Ass.*, 1970, *211*, 113. See also P. D. Reeme, *Hosp. Formul. Mgmt*, 1970, *5*, 15, per *Int. pharm. Abstr.*, 1973, *10*, 26.

Hypouricaemia (serum-urate concentrations of less than 20 μg per ml) in 6 patients could have been due to guaiphenesin. Therapeutic doses for 3 days reduced serum urate by up to 30 μg per ml in 4 patients.—C. M. Ramsdell and W. N. Kelley, *Ann. intern. Med.*, 1973, *78*, 239.

Absorption and Fate. Guaiphenesin is readily absorbed from the gastro-intestinal tract. It is rapidly metabolised and excreted in the urine.

Guaiphenesin was rapidly absorbed from the gastro-intestinal tract, blood concentrations of 1.4 μg per ml occurring 15 minutes after a dose of 600 mg in 3 healthy fasting men. It was rapidly eliminated from the circulation, having a half-life of 1 hour, and was not detectable in the blood after 8 hours.—W. R. Maynard and R. B. Bruce, *J. pharm. Sci.*, 1970, *59*, 1346.

The major urinary metabolite of guaiphenesin was identified as (*o*-methoxyphenoxy)lactic acid.—W. J. A. VandenHeuvel *et al.*, *J. pharm. Sci.*, 1972, *61*, 1997.

Uses. Guaiphenesin is reported to reduce the viscosity of tenacious sputum and is used as an expectorant in cough linctuses and tablets.

When given by mouth or by injection in large doses, guaiphenesin has a relaxant effect on skeletal muscle similar to that of mephenesin which it closely resembles structurally, but this effect is not produced by the doses normally employed in the treatment of cough.

tics

teine (2948-y)

: (*rINN*).
rahy[illegible]-2-oxo-3-thienyl)carbamoyl]methyl}thio)-
l. [illegible]
C_4S_2 [illegible].3.
4611-23-4.

ne is being studied for use as a mucolytic

---

dictyon (2012-e)

ı Balm; Yerba Santa.
8013-08-9.

:d leaves of *Eriodictyon californicum* (Hydrophyl-

:tyon has been used as an expectorant. It has :en used to mask the taste of bitter drugs.

ırations

of preparations are listed below; details are given in Part 3.

etary Preparations

ngredient preparations. *Ger.:* Mistelan†; *Ital.:* Bronco-

---

yl Cysteine Hydrochloride

k)

-2-amino-3-mercaptopropionate hydrochloride.
NO_2S,HCl = 185.7.
— *3411-58-3 (ethyl cysteine); 868-59-7 (ethyl ne hydrochloride).*

l cysteine hydrochloride is a mucolytic agent p.1059) used in the treatment of disorders of the rat[illegible]act associated with excessive or vis- mu[illegible] daily dose of 600 to 900 mg has been n by [illegible]uth in 2 or 3 divided doses.

parations

es of preparations are listed below; details are given in Part 3.

ıprietary Preparations

Fludixan†.

---

hyl Orthoformate (5618-t)

ır de Kay; Triethoxymethane. Triethyl orthoformate.
$H_{16}O_3$ = 148.2.
[illegible] — *122-51-0.*
rmacopoeias. In *Fr.*

ıyl orthoformate is a cough suppressant (see 059). It is reported to be a respiratory antispas-)dic and is administered by mouth or rectally.

eparations

mes of preparations are listed below; details are given in Part 3.

oprietary Preparations

lg.: Aethone; *Fr.:* Aethone.

ılti-ingredient preparations. *Switz.:* Rectoquintyl; Recto- ıntyl-Prométhazine.

---

edrilate (5619-x)

edrilate (*rINN*).
edrilatum; UCB-3928. 1-Methyl-3-morpholinopropyl perhy- ro-4-phenylpyran-4-carboxylate.
$C_{20}H_{29}NO_4$ = 347.5.
CAS — *23271-74-1.*

Pedri[illegible] is a cough suppressant (see p.1059) which ıas[illegible] iven by mouth as the maleate in doses of 50 m[illegible] ee to six times daily.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

S.Afr.: Corbar S; Dykatuss "S"†.

Multi-ingredient preparations. *Ger.:* Duotal†.

Fominoben Hydrochloride (5620-[illegible])

Fominoben Hydrochloride (*rINNM*).
PB-89. 3'-Chloro-2'-[N-methyl-*N*-(morpholinocarbonylmeth- yl)aminomethyl]benzanilide hydrochloride.
$C_{21}H_{24}ClN_3O_3.HCl$ = 438.4.
CAS — 18053-31-1 (fominoben); 24600-36-0 (fominoben hydrochloride).

Fominoben hydrochloride is a centrally acting cough suppressant (see p.1059) which is also report- ed to have respiratory stimulant properties. It is giv- en in doses of 160 mg two or three times daily by mouth; it has also been given by slow intravenous injection.

References.

1. Sasaki T, *et al.* Effects of the antitussive fominoben (PB89) on hypoxia in chronic obstructive lung disease: comparison with dextromethorphan using a double-blind method. *J Int Med Res* 1985; 13: 96–101.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Ger.: Noleptan†; *Ital.:* Terion†; *Spain:* Broncomenal†; Tasadon†; Tosifar.

Multi-ingredient preparations. *Ger.:* Broncho-Noleptan[illegible]

Glaucine (19251-g)

Boldine Dimethyl Ether; DL-832 (*dl*-glaucine phosphate); d- Glaucine; MDL-832 (*dl*-glaucine phosphate). DL-1,2,9,10-Te- tramethoxyaporphine.
$C_{21}H_{25}NO_4$ = 355.4.
CAS — *5630-11-5 (dl-glaucine); 73239-87-9 (dl-glaucine phosphate); 475-81-0 (d-glaucine); 5996-06-5 (d-glau- cine hydrobromide).*

Glaucine is a centrally acting cough suppressant (see p.1059) which has been studied as the phos- phate.

d-Glaucine has been used as the hydrobromide and the hydrochloride as a cough suppressant in eastern Europe. It has been obtained from *Glaucium flavum* (Papaveraceae).

References.

1. Redpath JBS, Pleuvry BJ. Double-blind comparison of the respiratory and sedative effects of codeine phosphate and (+)-glaucine phosphate in human volunteers. *Br J Clin Pharmacol* 1982; 14: 555–8.
2. Rühle KH, *et al.* Objective evaluation of dextromethorphan and glaucine as antitussive agents. *Br J Clin Pharmacol* 1984; 17: 521–4.
3. Gastpar H, *et al.* Efficacy and tolerability of glaucine as an antitussive agent. *Curr Med Res Opin* 1984; 9: 21–7.

Guacetisal (12801-w)

Guacetisal (*rINN*).
Acetylsalicylic Acid Guaiacol Ester. o-Methoxyphenyl salicylate acetate.
$C_{16}H_{14}O_5$ = 286.3.
CAS — *55482-89-8.*

Guacetisal has been used in respiratory disorders as an expectorant (see p.1059). It has also been used as an antipyretic to reduce fever, the more usual treatment of which is discussed on p.2. Doses of 500 mg have been administered by mouth two to three times daily. It has also been administered rectally.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Ital.: Balsacetil; Broncaspin; Guaiaspir; Guajabronc; Prontomesal.

Guaiacol (2016-z)

Guajacol; Methyl Catechol.
CAS — 90-05-1 (guaiacol); 553-17-3 (guaiacol carbonate); 60296-02-8 (calcium guaiacolglycolate); 4112-89-4 (guaiacol phenylacetate).
Pharmacopoeias. In *Belg., Fr.,* and *Swiss, Fr.* also includes Guaiacol Carbonate.

The main constituent of guaiacol is 2-methoxyphenol, $CH_3O.C_6H_4.OH$ = 124.1.

Guaiacol has disinfectant properties and has been used as an expectorant (see p.1059).

Adverse effects are similar to those of Phenol, p.1141.

A wide range of salts and derivatives of guaiacol have been used similarly including the carbonate, cinnamate, ethylglycolate, calcium and sodium glycolates, phenylacetate, and phenylbutyrate. See also Guaiphenesin, p.1069 and Potassium Guaiacolsulfonate, p.1074.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Ger.: Anastil†.

Multi-ingredient preparations. *Austral.:* Waterbury's Compound; *Belg.:* Baume Dalet; Ebexol†; Eucalyptine Le Brun; Eucalyptine Pholcodine Le Brun; Inalpin; *Canad.:* Creo-Rectal; Demo-Cineol†; Dolodent†; Omni-Tuss; Valda; *Eire:* Valda; *Fr.:* Baume Dalet; Biocalyptol; Bi-Qui-Nol; Bronchodermine; Bronchorectine au Citral; Camphocalyptol *Quinine*†; Camphocalyptol Simple†; Campho-*Pneumine*; Élixir Dupeyroux†; Essence Algérienne; Eucalyptine Aspirine Quinine†; Eucalyptine Le Brun; Eucalyptine Pholcodine; Eucalyptiospirine†; Gaiarsol; Pulmosérum; Rectophédrol; Sirop Boin; Tieucaly†; Valda; *Ger.:* Anastil Camphert; Anastil†; Cobed†; Dalet-Balsam; Pertix†; Transpulmin; Zynedo- B†; Zynedo-K†; *Ital.:* Auricovit†; Biopulmin†; Bronco Valda†; Eucaliptina; Fosfoguaiacol; Glicocinnaminat†; Guaiadomust†; Katasma Balsamico†; Lactocol; Lipobalsamo; Otocaina†; Otormon F (*Femminile*)†; *S.Afr.:* Cocilix†; *Spain:* Anginum†; Anuferin Balsamico†; Bimoxi Mucolitico; Bronco Aseptilex; Bronco Aseptilex Fuerte; Bronco Aseptilex Tetra†; Broncolitic†; Bronquimar; Bronquimar NF†; Bronquimar Vit A; Edusan Fte Rectal; Eucalyptospirine; Eucalyptospirine Lact; Maboterpen; Pulmo Grey Balsam; Pulmo Hidratol†; Tos Mar; *Switz.:* Bronchodermine; Bronchorectine; Carmol "blanche"†; Libérol; Rectoseptal-Néo Pholcodine; Rectoseptal-Néo simple; *UK:* Dragon Balm; Pulmo Bailly; Valda; *USA:* Methagual.

Guaiapate (12803-l)

Guaiapate (*USAN, rINN*).
MG-5454. 1-{2-[2-(2-o-Methoxyphenoxyethoxy)ethoxy]ethyl}piperidine.
$C_{18}H_{29}NO_4$ = 323.4.
CAS — *852-42-6.*

Guaiapate has been used as a cough suppressant. It is reported to have central actions.

Guaietolin (12795-v)

Guaietolin (*rINN*).
Glycerylguethol; Glyguetol. 3-(2-Ethoxyphenoxy)propane-1,2-diol.
$C_{11}H_{16}O_4$ = 212.2.
CAS — *63834-83-3.*

Guaietolin is an analogue of guaiphenesin which is used as an expectorant (see p.1059). It has been given by mouth in doses of 300 to 600 mg two to three times daily.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Fr.: Guéthural.

Guaimesal (1749-r)

Guaimesal (*rINN*).
(±)-2-(o-Methoxyphenoxy)-2-methyl-1,3-benzodioxan-4-one.
$C_{16}H_{14}O_5$ = 286.3.
CAS — *81674-79-5.*

Guaimesal is reported to have anti-inflammatory, antipyretic, analgesic, and mucolytic properties and has been given by mouth in a usual dose of 500 mg two to three times daily as an adjunct in the treatment of acute and chronic infections of the respiratory tract. It has also been administered rectally in suppositories.

Guaimesal has been reported to improve fever, cough frequency and intensity, and sputum viscosity in patients with acute or chronic bronchitis.[1] However, as stated in the discussion on the management of cough (see p.1059) mucolytics are generally considered t[illegible] more effective nonant[illegible] p.1567.

1. Jager EGH. Double-bl[illegible] tion of guaimesal in ou[illegible]

Preparations

Names of preparations a[illegible]

Proprietary Preparat[illegible]

Ital.: Bronteril.

Guaiphenesi[illegible]

Guaiphenesin (*BAN*).
Glyceryl Guaiacolate; [illegible] Ether; Guaiacyl Glyce[illegible] Guaifenesina; Guaifenc[illegible] 3-(2-Methoxyphenoxy[illegible]
$C_{10}H_{14}O_4$ = 198.2.
CAS — 93-14-1.
Pharmacopoeias. In *Au[illegible] Port., Swiss,* and *US.* The standards of *Ph. E[illegible]* ties to the Conventior[illegible] macopoeia, see p.xiii.

A white or slightly gr[illegible] a slight characteristic[illegible] BP **solubilities** are: s[illegible] cohol and in chlorofo[illegible] bilities are: soluble 1[illegible] in chloroform, and ir[illegible] glycerol. A 1% soluti[illegible] syrup has a pH of 2.5[illegible]

Adverse Effect

Gastro-intestinal [illegible] reported with gua[illegible] nausea and vomit[illegible]

Pharmacokine

Guaiphenesin is a[illegible] tract. It is metabo[illegible]

Uses and Adm

Guaiphenesin is [illegible] tenacious sputum[illegible] p.1059). It has be[illegible] to 400 mg every [illegible] may be given 10[illegible] dren aged 2 to 6[illegible] It has been used [illegible]

Infertility. Guaiph[illegible] tility in women wit[illegible] cervical mucus.[1] Th[illegible] mention of this use[illegible]

1. Check JH, *et al.* In[illegible] esin. *Fertil Steril* [illegible]

Respiratory disor[illegible]

tions available 'ove[illegible] in was an effective[illegible] discussed on p.105[illegible]

1. Thomas J. Guaiph[illegible] tive. *Aust J Pharm*[illegible]

Uricosuric actio[illegible]

rum-urate concentr[illegible] effect in these patie[illegible] ered to be clinically[illegible]

1. Ramsdell CM, *et* [illegible] *J Rheumatol* 1974[illegible]
2. Matheson CE, *et a*[illegible] tion on serum uric[illegible] 4.

Preparations

Names of preparatio[illegible]

Official Preparati[illegible]

USP 23: Dyphyllin[illegible] Guaifenesin Tablets[illegible] Guaifenesin and P[illegible] Guaifenesin Capsul[illegible] ride, and Dextrome[illegible] in Syrup; Guaifen[illegible] Capsules; Theophy[illegible]

Proprietary Prep[illegible]

Aust.: Guafen; My[illegible] er; *Austral.:* Robit[illegible] Expectorant; *Canad.* Expectorant; Resyl[illegible] posyrup expector[illegible] Nephulon G; Robit[illegible] Robitussin; *S.Afr.:*

The symbol † denotes a preparation no longer actively marketed

...tions

...Juice *(B.P.C. 1949)*. Succus Allii. Bruise garlic ...d express the juice; mix the marc with water ...d again express the liquid; repeat the operation ... volume of the mixed juice and washings ... to 80 ml, and add alcohol (90%) 20 ml; allow ... for 14 days, and decant or filter. *Dose*. 2 to ...

... Syrup *(B.P.C. 1949)*. Syr. Allii. Garlic juice ... sucrose 80 g, acetic acid (6 per cent) 20 ml, ... 20 ml. *Dose*. 2 to 8 ml.

...5-j

...delia *(B.P.C. 1949)*. Gum Plant; Gumweed; Tar ...

...copoeias. In *Belg*. and *Fr*. which also allow *G.* ..., *G. robusta*, and *G. squarrosa*. *Span*. and *Port*. ... *G. robusta; Port*. also allows *G. squarrosa*.

...dried leaves and flowering tops of *Grindelia campo-* ... (Compositae) containing not less than 20% of alco- ...(90%)-soluble extractive. **Store** in a cool dry place.

...delia has expectorant properties and has been stated ... exert a spasmolytic effect. It has been used as a ... extract or a tincture in the treatment of asthma ... bronchitis. Large doses sometimes cause renal dis-...ances. Its nauseous taste may be masked with chlo-... or glycerol.

...rations

...delia **Liquid Extract** *(B.P.C. 1949)*. Ext. Grindel. ... Grindelia 100 g is exhausted by percolation with ...hol (90%), the alcohol is removed by distillation, ... the residue is dissolved in water 50 ml to which ... g of sodium bicarbonate has previously been added; ... effervescence has ceased, the solution is adjusted to ... ml with alcohol (90%) and filtered. *Dose*. 0.6 to 2 ml.

...16-z

...iacol *(B.P.C. 1949)*. Gaïacol; Methyl Catechol.

CAS — 90-05-1 (2-methoxyphenol).

...rmacopoeias. In *Arg., Fr., It., Mex., Port., Roum.,* ..., and *Swiss.*

... colourless or almost colourless oily liquid or crystals ... a penetrating aromatic odour and a caustic taste, ...ained as a liquid by fractional distillation of wood-tar ...sote or, usually as crystals, by synthesis.

The main constituent is 2-methoxyphenol, $CH_3O.C_6H_4.OH$ = 124.1. Wt per ml (liquid) about 1.12 g; m.p. (crystals) about 28°. It tends to become ...llowish on exposure to light.

...uble 1 in 80 of water; miscible with alcohol, chloro-form, ether, glacial acetic acid, and fixed and volatile ...ils; soluble 1 in 1 of glycerol but separates out on the ...dition of water. **Incompatible** with ferric salts, ...mphor, menthol, and chloral hydrate. **Protect** from light.

...aiacol has disinfectant properties similar to those of ...sote. It has been used as an expectorant in doses of 0.3 to 0.6 ml. Adverse effects are similar to those of Phenol, p.571.

...017-c

...iacol Carbonate *(B.P.C. 1949)*. Duotal. Bis(2-met-...hyphenyl) carbonate.
$(CH_3O.C_6H_4.O)_2.CO$=274.3.

CAS — 553-17-3.

...rmacopoeias. In *Port*. and *Span*.

...iacol carbonate is the carbonic ester of guaiacol. It ... a white, almost odourless, tasteless, crystalline ...der. M.p. 83° to 88°. Practically **insoluble** in water; ...uble 1 in 70 of alcohol and 1 in 20 of ether; readily ...uble in chloroform; slightly soluble in glycerol and ...ed oils. It is decomposed by alcoholic potassium hydroxide solution and guaiacol separates from the solu-...tion on the addition of excess acid.

...iacol carbonate has the actions of guaiacol but is ... irritant. It has been used in doses of 0.3 to 1 g. It ...erates guaiacol slowly and incompletely in the intestines, the larger part passing through the alimentary tract unchanged.

2018-k

Guaiphenesin *(B.P.)*. Guaiacyl Glyceryl Ether; Guaiacol Glycerol Ether; Guaifenesin *(U.S.P.)*; Glyceryl Guaiacolate; Glycerylguayacolum; Guajacolum Glycerolatum. 3-(2-Methoxyphenoxy)propane-1,2-diol.
$C_{10}H_{14}O_4$=198.2.

CAS — 93-14-1.

Pharmacopoeias. In *Aust., Br., Cz., Roum.*, and *U.S.*

White or slightly grey crystals or crystalline aggregates, odourless or with a slight characteristic odour and with a bitter taste. M.p. 78° to 82° with a range of not more than 3°.

Soluble 1 in 33 of water at 20°, 1 in 11 of alcohol and of chloroform, and 1 in 100 of ether; soluble 1 in 15 of glycerol with warming, 1 in 15 of propylene glycol, and 1 in 80 of sorbitol syrup. A 2% solution in water has a pH of 5 to 7. Aqueous solutions are stable and may be **sterilised** by autoclaving. **Store** in airtight containers.

Adverse Effects and Precautions. Gastro-intestinal discomfort and drowsiness have been reported. Very large doses cause nausea and vomiting.

A metabolite of guaiphenesin was found to produce an apparent increase in urinary 5-hydroxyindoleacetic acid, and guaiphenesin could thus interfere with the diagnosis of the carcinoid syndrome. Patients being evaluated for the carcinoid syndrome should therefore discontinue any preparation containing guaiphenesin for 24 hours before the collection of urine specimens for the determination of 5-hydroxy indoleacetic acid. Acetanilide, mephenesin, and methocarbamol had been reported to cause similar false positive reactions, and hexamine mandelate and some phenothiazine derivatives to cause false negative reactions.— A. T. Pedersen *et al.*, *J. Am. med. Ass.*, 1970, *211*, 1184. See also P. D. Reeme, *Hosp. Formul. Mgmt*, 1970, *5*, 15, per *Int. pharm. Abstr.*, 1973, *10*, 26.

Hypouricaemia (serum-urate concentrations of less than 20 µg per ml) in 6 patients could have been due to guaiphenesin. Therapeutic doses for 3 days reduced serum urate by up to 30 µg per ml in 4 patients.— C. M. Ramsdell and W. N. Kelley, *Ann. intern. Med.*, 1973, *78*, 239.

Absorption and Fate. Guaiphenesin is readily absorbed from the gastro-intestinal tract. It is rapidly metabolised and excreted in the urine.

Guaiphenesin was rapidly absorbed from the gastro-intestinal tract, blood concentrations of 1.4 µg per ml occurring 15 minutes after a dose of 600 mg in 3 healthy fasting men. It was rapidly eliminated from the circulation, having a half-life of 1 hour, and was not detectable in the blood after 8 hours.— W. R. Maynard and R. B. Bruce, *J. pharm. Sci.*, 1970, *59*, 1346.

The major urinary metabolite of guaiphenesin was indentified as β-(2-methoxyphenoxy)lactic acid.— W. J. A. VandenHeuvel *et al.*, *J. pharm. Sci.*, 1972, *61*, 1997.

Uses. Guaiphenesin is reported to reduce the viscosity of tenacious sputum and is used as an expectorant. It has been given in doses of 100 to 200 mg every 2 to 4 hours.

When given by mouth or by injection in large doses, guaiphenesin has a relaxant effect on skeletal muscle similar to that of mephenesin which it closely resembles structurally, but this effect is not produced by the doses normally employed in the treatment of cough.

Guaiphenesin was no better than water in lowering the viscosity of 27 sputum specimens obtained from chronic bronchitics. Doses of 0.8 to 1.6 g daily had no effect on sputum or respiratory function when compared with placebo in 11 patients with chronic bronchitis.— S. R. Hirsch *et al.*, *Chest*, 1973, *63*, 9.

From a study in 239 patients it was reported that guaiphenesin reduced cough frequency and intensity in patients with dry or productive cough, and helped to thin sputum, when compared to placebo.— R. E. Robinson *et al.*, *Robins*, *Curr. ther. Res.*, 1977, *22*, 284.

A report of a double-blind crossover study in 19 patients with chronic bronchitis showed that guaiphenesin was not significantly better that a placebo in aiding clearance of secretion from the lungs.— D. B. Yeates *et al.*, *Am. Rev. resp. Dis.*, 1977, *115*, *Suppl.* 4, 182.

Effects on blood. A dose of 200 mg of guaiphenesin was found to prolong the activated-plasma clotting time in 22 healthy volunteers. The same dose, given to 12 healthy volunteers, was found to reduce platelet adhesiveness significantly.— R. D. Eastham and E. P. Griffiths, *Lancet*, 1966, *1*, 795.

Guaiphenesin 200 mg given as a single dose to 5 healthy subjects was associated with transient abnormality in platelet aggregation patterns determined 1 hour after ingestion, showing some inhibition of secondary aggregation but less marked than that observed in other subjects given chlorpromazine or aspirin. Mean bleeding times as determined by a modified Ivy technique were prolonged by single doses of aspirin but were not affected by guaiphenesin; thrice-daily doses of indomethacin given for 3 days caused some prolongation.— G. R. Buchanan *et al.*, *Am. J. clin. Path.*, 1977, *68*, 355.

Preparations

Guaifenesin Capsules *(U.S.P.)*. Capsules containing guaiphenesin. Store in airtight containers.

Guaifenesin Syrup *(U.S.P.)*. A syrup containing guaiphenesin and alcohol 3 to 4%. pH 2.3 to 3. Store in airtight containers.

Guaifenesin Tablets *(U.S.P.)*. Tablets containing guaiphenesin. Store in airtight containers.

Guaiphenesin Linctuses. (1) *Lemon-flavoured*. Guaiphenesin 2 g, glycerol 10 ml, chloroform spirit 10 ml, menthol 10 mg, compound tartrazine solution 0.2 ml, water 10 ml, modified lemon syrup to 100 ml.
(2) *Tolu-flavoured*. Guaiphenesin 2 g, glycerol 10 ml, chloroform spirit 10 ml, menthol 10 mg, amaranth solution 1 ml, tolu solution 10 ml, invert syrup 20 ml, syrup to 100 ml.
Modified lemon syrup contains lemon spirit 0.5 ml, citric acid monohydrate 2.5 g, invert syrup 20 ml, syrup to 100 ml.

Both lemon-flavoured and tolu-flavoured guaiphenesin linctuses remained stable for 6 months when stored at temperatures from −5° to 37°.— Pharm. Soc. Lab. Rep. No. P/65/21, 1965. See also G. Smith, *Pharm. J.*, 1966, *1*, 165.

Proprietary Preparations

Dimotane Expectorant *(Robins, UK)*. Contains in each 5 ml guaiphenesin 100 mg, brompheniramine maleate 2 mg, phenylephrine hydrochloride 5 mg, and phenylpropanolamine hydrochloride 5 mg (suggested diluent, syrup). **Dimotane Expectorant DC** contains in addition hydrocodone tartrate 1.8 mg in each 5 ml. *Dose*. 5 to 10 ml four times daily; children, 1 to 3 years, 1 to 2.5 ml; 3 to 6 years, 2.5 to 5 ml; 6 to 12 years, 5 ml.

Dimotane with Codeine *(Robins, UK)*. Contains in each 5 ml guaiphenesin 100 mg, codeine phosphate 10 mg, brompheniramine maleate 2 mg, phenylephrine hydrochloride 5 mg, and phenylpropanolamine hydrochloride 5 mg (suggested diluent, syrup). For cough. *Dose*. 5 to 10 ml four times daily.

Dimotane with Codeine Paediatric *(Robins, UK)*. Contains in each 5 ml guaiphenesin 50 mg, codeine phosphate 3 mg, brompheniramine maleate 1 mg, phenylephrine hydrochloride 2.5 mg, and phenylpropanolamine hydrochloride 2.5 mg (suggested diluent, syrup). *Dose*. 3 to 6 years, 5 ml four times daily; 6 to 12 years, 5 to 10 ml.

Exyphen *(Norton, UK: Vestric, UK)*. An elixir containing in each 5 ml guaiphenesin 80 mg, brompheniramine maleate 2 mg, phenylephrine hydrochloride 4.75 mg, and phenylpropanolamine hydrochloride 5 mg. For cough. *Dose*. 5 to 10 ml four times daily; children, 2.5 to 5 ml three or four times daily.

Noradran Bronchial Syrup *(Norma, UK: Farillon, UK)*. Contains in each 5 ml guaiphenesin 25 mg, diphenhydramine hydrochloride 5 mg, diprophylline 50 mg, and ephedrine hydrochloride 7.5 mg. *Dose*. 10 ml every 4 hours; children over 5 years, 5 ml.

Pholcomed Expectorant (formerly known as Pulmodrine Expectorant) *(Medo Chemicals, UK)*. Contains in each 5 ml guaiphenesin 62.5 mg and methylephedrine hydrochloride 625 µg. *Dose*. 10 to 20 ml thrice daily; children, 2.5 to 5 ml.

Robitussin *(Robins, UK)*. An expectorant mixture containing in each 5 ml guaiphenesin 100 mg (suggested diluent, syrup). (Also available as Robitussin in *Austral., Canad., Ital.*).

Robitussin AC *(Robins, UK)*. Contains in each 5 ml guaiphenesin 100 mg, codeine phosphate 10 mg, and pheniramine maleate 7.5 mg (suggested diluent, syrup). For coughs. *Dose*. 5 to 10 ml four times daily; children, 6 to 12 years, 5 ml.

A. INGREDIENT NAME:

HYDRAZINE SULFATE

B. Chemical Name:

Hydrazinium Sulfate, Hydrazonium Sulfate

C. Common Name:

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

	(Specifications)	*(Results)*
Assay:	99.0% min.	99.3%

E. Information about how the ingredient is supplied:

White Crystalline Powder

F. Information about recognition of the substance in foreign pharmacopeias:

USP 23, Indian Pharmacopeia 3rd Ed.

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Gold, J. Use of Hydrazine Sulfate in terminal and Preterminal Cancer patients: results of investigational new drug (IND) study in 84 valuable patients. *Oncology.* 1975; 32(1): 1-10

Chlebowski, R. T., Bulcavage, L., and Grosvenor, M. Hydrazine Sulfate in Cancer patients with weight loss. A placebo-controlled clinical experience. *Cancer.* 1987; 59(3): 406-410.

Bairam, A. Theophylline versus caffeine: comparative effects in treatment of idiopathic apnea in the preterm infant. *J. Pediatr.* 1987; 110:636.

Eisenberg, M. G. and Kang, N. Stability of citrated caffeine solutions for injectable and external use. *Am. J. Hosp. Pharm.* 1984;41:2405.

H. Information about dosage forms used:

I. Information about strength:

60mg, 3 times/d

J. Information about route of administration:

Orally

K. Stability data:

Melts at about 254°
Oxidizing Agents
Bases

L. Formulations:

M. Miscellaneous Information:

50-1876
#49320

CERTIFICATE OF ANALYSIS

PRODUCT: HYDRAZINE SULFATE REAGENT
RELEASE #: N

LOT # :L609141

GRADE: A.C.S.
CODE:G61024

		SPECIFICATIONS	RESULT
1.	DESCRIPTION	WHITE CRYSTALLINE POWDER E	CONFORMS
2.	Identification	To pass test	Passes test
3.	Residue on Ignition	0.05% max.	0.01%
4.	Insoluble matter	0.005% max.	0.0025%
5.	Assay	99.0% min.	99.3% D
6.	Heavy Metals	0.002% max.	< 0.001%
7.	Chloride	0.005% max.	0.002%
8.	Iron	0.001% max.	< 0.0003%

ATTENTION: TONY HATCHETT

Date :04/09/97

Prepared by : A. HAZARI

Approved by : 4/97

10690

QUALITY CONTROL REPORT

CHEMICAL NAME.: HYDRAZINE SULFATE A.C.S.REAGENT

MANUFACTURE LOT NO.: 609141

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP__/BP__/MERCK__/NF__/MART.__/CO.SPECS.__.

1) DESCRIPTION.:
WHITE TO ORTHORHOMBIC CRYSTALS.GLASS-LIKE PLATES OR PRISMS.

2) SOLUBILITY.:
SOLUBLE IN ABOUT 33 PARTS OF COLD WATER;FREELY SOLUBLE IN HOT WATER.INSOLUBLE IN ALCOHOL.

3) MELTING POINT.:
MELTS AT ABOUT 254 degree. K

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:
A) A SOLUTION RESPONDS TO THE TESTS FOR SULFATE.

PASSES.: _____ **FAILS.:** _____

COMMENTS.:

ANALYST SIGNATURE.: _____ **DATE.:** _____

PREPACK TEST.: _____ **DATE.:** _____ **INITIAL.:** _____

RETEST.: _____ **DATE.:** _____ **INITIAL.:** _____

Use your web browser's "Back" key to return to previous topic.

Hydrazine Sulfate

****** MATERIAL SAFETY DATA SHEET ******

Hydrazine Sulfate
11070

**** SECTION 1 - CHEMICAL PRODUCT AND COMPANY IDENTIFICATION ****

MSDS Name: Hydrazine Sulfate
Catalog Numbers:
H320 500, H320-500, H320500
Synonyms:
Diamine Sulfate; Hydrazine Monosulfate; Hydrazinium Sulfate.
Company Identification: Fisher Scientific
1 Reagent Lane
Fairlawn, NJ 07410
For information, call: 201-796-7100
Emergency Number: 201-796-7100
For CHEMTREC assistance, call: 800-424-9300
For International CHEMTREC assistance, call: 703-527-3887

**** SECTION 2 - COMPOSITION, INFORMATION ON INGREDIENTS ****

CAS#	Chemical Name	%	EINECS#
10034-93-2	HYDRAZINE SULFATE	>99	233-110-4

Hazard Symbols: T
Risk Phrases: 23/24/25 43 45

**** SECTION 3 - HAZARDS IDENTIFICATION ****

EMERGENCY OVERVIEW

Appearance: white.
Danger! Corrosive. Carcinogen. May be harmful if swallowed. Sensitizer. May cause lung damage. May cause severe eye irritation and possible injury. May cause liver and kidney damage. May cause severe skin irritation and possible burns. May cause severe respiratory and digestive tract irritation with possible burns. May cause cancer based on animal studies. Material is shock sensitive and potentially explosive.
Target Organs: Blood, kidneys, central nervous system, liver.

Potential Health Effects
Eye:
Contact with eyes may cause severe irritation, and possible eye burns. May cause eye injury.
Skin:
May cause skin sensitization, an allergic reaction, which becomes

evident upon re-exposure to this material. May cause severe skin irritation with possible burns, especially if skin is wet or moist.

Ingestion:
May cause liver and kidney damage. May cause severe digestive tract irritation with abdominal pain, nausea, vomiting and diarrhea. May cause corrosion and permanent tissue destruction of the esophagus and digestive tract. Exposure may cause anemia and other blood abnormalities. May be harmful if swallowed.

Inhalation:
Irritation may lead to chemical pneumonitis and pulmonary edema. May cause liver and kidney damage. May cause severe irritation of the upper respiratory tract with pain, burns, and inflammation. May cause effects similar to those described for ingestion.

Chronic:
Prolonged or repeated skin contact may cause sensitization dermatitis and possible destruction and/or ulceration. May cause liver and kidney damage. May cause cancer according to animal studies. May cause digestive tract disturbances.

**** SECTION 4 - FIRST AID MEASURES ****

Eyes:
Immediately flush eyes with plenty of water for at least 15 minutes, occasionally lifting the upper and lower lids. Get medical aid immediately.

Skin:
Get medical aid immediately. Immediately flush skin with plenty of soap and water for at least 15 minutes while removing contaminated clothing and shoes.

Ingestion:
Do NOT induce vomiting. If victim is conscious and alert, give 2-4 cupfuls of milk or water. Get medical aid immediately.

Inhalation:
Get medical aid immediately. Remove from exposure to fresh air immediately. If not breathing, give artificial respiration. If breathing is difficult, give oxygen.

Notes to Physician:
Treat symptomatically and supportively.

Antidote:
No specific antidote exists.

**** SECTION 5 - FIRE FIGHTING MEASURES ****

General Information:
As in any fire, wear a self-contained breathing apparatus in pressure-demand, MSHA/NIOSH (approved or equivalent), and full protective gear. Dusts at sufficient concentrations can form explosive mixtures with air. Combustion generates toxic fumes. Material is shock sensitive and potentially explosive. Greatly increases the burning rate of combustible materials. Violently decomposes when heated under confinement.

Extinguishing Media:
For small fires, use water spray, dry chemical, carbon dioxide or chemical foam.

Autoignition Temperature: Not applicable.
Flash Point: Not applicable.
NFPA Rating: Not published.
Explosion Limits, Lower: Not available.
Upper: Not available.

**** SECTION 6 - ACCIDENTAL RELEASE MEASURES ****

General Information: Use proper personal protective equipment as indicated in Section 8.

Spills/Leaks:
Sweep up, then place into a suitable container for disposal. Avoid generating dusty conditions.

**** SECTION 7 - HANDLING and STORAGE ****

Handling:
Wash thoroughly after handling. Remove contaminated clothing and

wash before reuse. Use with adequate ventilation. Minimize dust generation and accumulation. May form flammable dust-air mixtures. Loosen closure cautiously before opening. Do not get on skin and clothing. Empty containers retain product residue, (liquid and/or vapor), and can be dangerous. Do not ingest or inhale. Avoid mechanical shock and friction. Do not pressurize, cut, weld, braze, solder, drill, grind, or expose empty containers to heat, sparks or open flames.

Storage:

Keep away from heat, sparks, and flame. Do not store near combustible materials. Store in a tightly closed container. Store in a cool, dry, well-ventilated area away from incompatible substances.

**** SECTION 8 - EXPOSURE CONTROLS, PERSONAL PROTECTION ****

Engineering Controls:

Use process enclosure, local exhaust ventilation, or other engineering controls to control airborne levels.

Exposure Limits

Chemical Name	ACGIH	NIOSH	OSHA - Final PELs
HYDRAZINE SULFATE	none listed	none listed	none listed

OSHA Vacated PELs:

HYDRAZINE SULFATE:

No OSHA Vacated PELs are listed for this chemical.

Personal Protective Equipment

Eyes:

Wear appropriate protective eyeglasses or chemical safety goggles as described by OSHA's eye and face protection regulations in 29 CFR 1910.133.

Skin:

Wear appropriate protective gloves to prevent skin exposure.

Clothing:

Wear appropriate protective clothing to prevent skin exposure.

Respirators:

Follow the OSHA respirator regulations found in 29CFR 1910.134. Always use a NIOSH-approved respirator when necessary.

**** SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES ****

Physical State:	Solid
Appearance:	white
Odor:	None reported.
pH:	1.3 (0.2M solution)
Vapor Pressure:	Negligible.
Vapor Density:	Not applicable.
Evaporation Rate:	Negligible.
Viscosity:	Not available.
Boiling Point:	Not available.
Freezing/Melting Point:	489 deg F
Decomposition Temperature:	Not available.
Solubility:	Soluble in water.
Specific Gravity/Density:	1.4 (water=1)
Molecular Formula:	H4N2.H2SO4
Molecular Weight:	130.12

**** SECTION 10 - STABILITY AND REACTIVITY ****

Chemical Stability:

Stable under normal temperatures and pressures. Substance is shock sensitive and thermally unstable.

Conditions to Avoid:

Mechanical shock, incompatible materials, temperatures above 160°C.

Incompatibilities with Other Materials:
Oxidizing agents, combustible materials, sodium amide.
Hazardous Decomposition Products:
Nitrogen oxides, carbon monoxide, oxides of sulfur, carbon dioxide.
Hazardous Polymerization: Has not been reported.

**** SECTION 11 - TOXICOLOGICAL INFORMATION ****

RTECS#:
CAS# 10034-93-2: MV9625000
LD50/LC50:
CAS# 10034-93-2: Oral, mouse: LD50 = 740 mg/kg; Oral, rat: LD50 = 601 mg/kg.
Carcinogenicity:
HYDRAZINE SULFATE -
California: carcinogen
NTP: Suspect carcinogen
OSHA: Possible Select carcinogen
Epidemiology:
Oral and intraperitoneal administration of hydrazine salts t o animals have produced lung and liver carcinomas.
Teratogenicity:
No information available.
Reproductive Effects:
No information available.
Neurotoxicity:
No information available.
Mutagenicity:
Please refer to RTECS# MV9625000 for specific information.
Other Studies:
Skin irritation, guinea pig: slight. Eye irritation, rabbit: severe.

**** SECTION 12 - ECOLOGICAL INFORMATION ****

Ecotoxicity:
No information available.
Environmental Fate:
No information reported.
Physical/Chemical:
No information available.
Other:
None.

**** SECTION 13 - DISPOSAL CONSIDERATIONS ****

Dispose of in a manner consistent with federal, state, and local regulations.
RCRA D-Series Maximum Concentration of Contaminants: Not listed.
RCRA D-Series Chronic Toxicity Reference Levels: Not listed.
RCRA F-Series: Not listed.
RCRA P-Series: Not listed.
RCRA U-Series: Not listed.
Not listed as a material banned from land disposal according to RCRA.

**** SECTION 14 - TRANSPORT INFORMATION ****

US DOT
Shipping Name: CORROSIVE SOLID,ACIDIC,INORGANIC,N.O.S. (HYDRAZINE SULFATE)
Hazard Class: 8
UN Number: UN3260
Packing Group: II
IMO
No information available.
IATA
No information available.
RID/ADR
No information available.
Canadian TDG
Shipping Name: CORROSIVE SOLIDS NOS (HYDRAZINE SULFATE)
Hazard Class: 8(9.2)
UN Number: UN1759

**** SECTION 15 - REGULATORY INFORMATION ****

US FEDERAL

TSCA

CAS# 10034-93-2 is listed on the TSCA inventory.

Health & Safety Reporting List

None of the chemicals are on the Health & Safety Reporting List.

Chemical Test Rules

None of the chemicals in this product are under a Chemical Test Rule.

Section 12b

None of the chemicals are listed under TSCA Section 12b.

TSCA Significant New Use Rule

None of the chemicals in this material have a SNUR under TSCA.

SARA

Section 302 (RQ)

None of the chemicals in this material have an RQ.

Section 302 (TPQ)

None of the chemicals in this product have a TPQ.

SARA Codes

CAS # 10034-93-2: acute, chronic, reactive.

Section 313

This material contains HYDRAZINE SULFATE (CAS# 10034-93-2, >99%),which is subject to the reporting requirements of Section 313 of SARA Title III and 40 CFR Part 373.

Clean Air Act:

This material does not contain any hazardous air pollutants.
This material does not contain any Class 1 Ozone depletors.
This material does not contain any Class 2 Ozone depletors.

Clean Water Act:

None of the chemicals in this product are listed as Hazardous Substances under the CWA.
None of the chemicals in this product are listed as Priority Pollutants under the CWA.
None of the chemicals in this product are listed as Toxic Pollutants under the CWA.

OSHA:

None of the chemicals in this product are considered highly hazardous by OSHA.

STATE

HYDRAZINE SULFATE can be found on the following state right to know lists: New Jersey, Florida, Pennsylvania, Minnesota, Massachusetts.
The following statement(s) is(are) made in order to comply with the California Safe Drinking Water Act:
WARNING: This product contains HYDRAZINE SULFATE, a chemical known to the state of California to cause cancer.
California No Significant Risk Level:
CAS# 10034-93-2: no significant risk level = 0.2 ug/day

European/International Regulations

European Labeling in Accordance with EC Directives

Hazard Symbols: T

Risk Phrases:

R 23/24/25 Toxic by inhalation, in contact with skin and if swallowed.
R 43 May cause sensitization by skin contact.
R 45 May cause cancer.

Safety Phrases:

S 44 If you feel unwell, seek medical advice (show the label where possible).
S 53 Avoid exposure - obtain special instructions before use.

WGK (Water Danger/Protection)

CAS# 10034-93-2:

Canada

CAS# 10034-93-2 is listed on Canada's DSL/NDSL List.
This product has a WHMIS classification of D2A, E.
CAS# 10034-93-2 is not listed on Canada's Ingredient Disclosure List.

Exposure Limits

**** SECTION 16 - ADDITIONAL INFORMATION ****

MSDS Creation Date: 9/22/1995 Revision #3 Date: 9/02/1997

The information above is believed to be accurate and represents the best information currently available to us. However, we make no warranty of merchantability or any other warranty, express or implied, with respect to such information, and we assume no liability resulting from its use. Users should make their own investigations to determine the suitability of the information for their particular purposes. In no way shall Fisher be liable for any claims, losses, or damages of any third party or for lost profits or any special, indirect, incidental, consequential or exemplary damages, howsoever arising, even if Fisher has been advised of the possibility of such damages.

Spectral purity—Measure in a 1-cm cell at 300 nm, with a suitable spectrophotometer, against air as the blank: its absorbance is not more than 0.08.

Hexanes (suitable for use in ultraviolet spectrophotometry); usually a mixture of several isomers of hexane (C_6H_{14}), predominantly *n*-hexane, and methylcyclopentane (C_6H_{12})—Use ACS reagent grade.

Hexanitrodiphenylamine (*Dipicrylamine*), $C_{12}H_5N_7O_{12}$—**439.21**—Yellow-gold powder or prisms. *Explosive.* Usually contains about 15% of water as a safety precaution. Insoluble in water, in alcohol, in acetone, and in ether; soluble in glacial acetic acid and in alkalies.

Water, Method I ⟨921⟩: not more than 16%.

Hexanophenone, $C_{12}H_{16}O$—**176.26**—Yellow liquid.

Assay—Inject an appropriate specimen into a suitable gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 30-m × 0.25-mm capillary column coated with a 1-μm layer of phase G3; the injection port temperature is maintained at 280°; the detector temperature is maintained at 300°; the column temperature is maintained at 180° and programmed to rise 10° per minute to 280°. The area of the $C_{12}H_{16}O$ peak is not less than 98% of the total peak area.

Refractive index ⟨831⟩: 1.511 ± 0.002 at 20°.

Hexokinase and Glucose-6-phosphate Dehydrogenase Suspension—Use a suitable grade.[1]

Suitability—When used in the assay of lactulose, determine that a suitable absorbance-versus-concentration slope is obtained, using USP Lactulose RS, the reagent blank absorbance being not more than 0.020.

Histamine Dihydrochloride, $C_5H_9N_3 \cdot 2HCl$—**184.07**—Use USP Histamine Dihydrochloride RS.

Hydrazine Hydrate, 85% in Water, $(NH_2)_2 \cdot H_2O$—**50.06**—Colorless liquid.

Assay—Transfer 600 mg, accurately weighed, to a 100-mL volumetric flask. Dilute with water to volume, and mix. Pipet 10 mL into a suitable beaker, add 1.0 g of sodium bicarbonate and 50.0 mL of 0.1 *N* iodine VS. Titrate the excess iodine with 0.1 *N* sodium thiosulfate VS, using starch TS as the indicator. Perform a blank determination, and make any necessary correction. Each mL of 0.1 *N* iodine is equivalent to 12.52 mg of $(NH_2)_2 \cdot H_2O$. Not less than 83% is found.

Hydrazine Dihydrochloride, $(NH_2)_2 \cdot 2HCl$—**104.97**—White powder.

Assay—Dissolve about 34 mg, accurately weighed, in 50 mL of water. Add carefully while stirring, 1 g of sodium bicarbonate. [*Caution—There may be a rapid evolution of carbon dioxide.*] Titrate with 0.1 *N* iodine solution, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary corrections. Each mL of 0.1 *N* iodine solution is equivalent to 2.63 mg of $(NH_2)_2 \cdot 2HCl$. Not less than 98% is found.

Hydrazine Sulfate, $(NH_2)_2 \cdot H_2SO_4$—**130.13**—Use ACS reagent grade.

Hydriodic Acid, HI—**127.91**—Use ACS reagent grade (containing not less than 47.0% of HI).

NOTE—For *Methoxy Determination* (see ⟨431⟩), use hydriodic acid that is labeled "for alkoxyl determination," or that is purified as directed under *Methoxy Determination* ⟨431⟩. Use this grade also for alkoxyl determinations in assays in the individual monographs.

Hydrochloric Acid, HCl—**36.46**—Use ACS reagent grade.

Hydrochloric Acid, Diluted (10 percent)—Prepare by mixing 226 mL of hydrochloric acid with sufficient water to make 1000 mL.

Hydrofluoric Acid, HF—**20.01**—Use ACS reagent grade.

Hydrogen Peroxide, 30 Percent, H_2O_2—**34.01**—Use ACS reagent grade.

Hydrogen Peroxide Solution—Use *Hydrogen Peroxide Topical Solution.*

Hydrogen Sulfide, H_2S—**34.08**—Colorless, poisonous gas, heavier than air. Soluble in water. Is generated by treating ferrous sulfide with diluted sulfuric or diluted hydrochloric acid. Other sulfides yielding hydrogen sulfide with diluted acids may be used. Is also available in compressed form in cylinders.

Hydrogen Sulfide Detector Tube—A fuse-sealed glass tube so designed that gas may be passed through it and containing suitable absorbing filters and support media for the indicator, the latter consisting of a suitable lead salt.

NOTE—A suitable detector tube that conforms to the monograph specification is available from National Draeger, Inc., P.O. Box 120, Pittsburgh, PA 15230-0120 as Reference Number 67 19001, Measuring Range 1 to 20 ppm. Tubes having conditions other than those specified in the monograph may be used in accordance with the section entitled *Tests and Assays* in the *General Notices.*

Hydroquinone, $C_6H_4(OH)_2$—**110.11**—Fine, colorless or white, needle crystals. Darkens on exposure to air and light. Soluble in water, in alcohol, and in ether.

Assay—Weigh accurately about 250 mg, and dissolve in a mixture of 100 mL of water and 10 mL of 0.1 *N* sulfuric acid in a 250-mL conical flask. Add 3 drops of a 1 in 100 solution of diphenylamine in sulfuric acid, and titrate with 0.1 *N* ceric sulfate VS until the solution is red-violet in color. Each mL of 0.1 *N* ceric sulfate is equivalent to 5.506 mg of $C_6H_4(OH)_2$. Not less than 99% is found.

Melting range ⟨741⟩: between 172° and 174°.

3′-Hydroxyacetophenone, $C_8H_8O_2$—**136.15**—Light brown powder chips and chunks. Melts at about 96°. Sparingly soluble in chloroform, yielding a clear, light yellow solution.

Assay—Inject an appropriate specimen into a suitable gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with G1; the detector and the injection port temperature are maintained at 300°; the column temperature is maintained at 180° and programmed to rise 10° per minute to 280° and held at that temperature for 10 minutes. The area of the main peak is not less than 97% of the total peak area.

4′-Hydroxyacetophenone, $HOC_6H_4COCH_3$—**136.15**—Gray powder, melting at about 109°.

***p*-Hydroxybenzoic Acid,** $C_7H_6O_3$—**138.12**—White crystals.

Assay—Transfer about 700 mg, accurately weighed, to a suitable container, and dissolve in 50 mL of acetone. Add 100 mL of water, mix, and titrate with 0.5 *N* sodium hydroxide VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 0.5 *N* sodium hydroxide is equivalent to 69.06 mg of $C_7H_6O_3$: not less than 97% is found.

Melting range ⟨741⟩: over a range of 2° that includes 216°.

4-Hydroxybenzoic Acid Isopropyl Ester, $HOC_6H_4COOCH(CH_2)_2$—**180.20**—Use a suitable grade.[32]

Melting range ⟨741⟩: between 84° and 87°.

1-Hydroxybenzotriazole Hydrate, $C_6H_5N_3O \cdot xH_2O$—**135.13** (anhydrous)—White crystalline powder. Sparingly soluble in alcohol yielding a clear, pale yellow solution.

2-Hydroxybenzyl Alcohol, $C_7H_8O_2$—**124.14**—Off-white flakes. Very soluble in alcohol, in chloroform, and in ether; soluble in 15 parts water and in benzene.

Assay—Inject an appropriate specimen into a gas chromatograph (see *Chromatography* ⟨621⟩), equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-μm layer of phase G2; the injection port temperature is maintained at 250°; the detector temperature is maintained at 300°; and the column temperature is maintained at 150° and programmed to rise 10° per minute to 280°. The area of the $C_7H_8O_2$ peak is not less than 99% of the total peak area.

Melting range ⟨741⟩: between 83° and 85°.

4-Hydroxyisophthalic Acid, $C_8H_6O_4$—**182.13**—Colorless branched needles. Freely soluble in alcohol and in ether.

Melting range ⟨741⟩: between 314° and 315°, with decomposition.

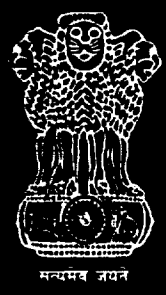
 Government of India
Ministry of Health & Family Welfare

Pharmacopoeia of India

(The Indian Pharmacopoeia)

Volume – II
(Q – Z & Appendices)

Third Edition



PUBLISHED BY THE CONTROLLER OF PUBLICATIONS, DELHI

1985

A fraction from petroleum containing about 90 per cent of *n*-hexane.

DESCRIPTION – Colourless, mobile, highly flammable liquid.

DISTILLATION RANGE – Not less than 95 per cent, distils between 67° and 70°, Appendix 5.3.

WT. PER ML – At 20°, 0.670 to 0.677 g, Appendix 5.19.

NON-VOLATILE MATTER – When evaporated on a water-bath and dried to constant weight at 105°, leaves not more than 0.01 per cent w/v of residue.

Histamine Acid Phosphate

Of the Indian Pharmacopoeia.

Histamine Dihydrochloride : $C_5H_9N_3,2HCl = 184.07$

DESCRIPTION – White crystalline powder.

SOLUBILITY – Freely soluble in *water* and in *methyl alcohol*; soluble in *alcohol*.

MELTING POINT – About 250°, Appendix 5.11.

DL-Histidine Monohydrochloride

$N{:}CH.NH.CH{:}C.CH_2.CH(NH_2).COOH,HCl = 191.62$

Contains not less than 99.0 per cent of $C_6H_9N_3O_2,HCl$, calculated with reference to the substance dried to constant weight at 105°.

DESCRIPTION – White, crystalline powder.

SOLUBILITY – Soluble in *water*.

LOSS ON DRYING – Loses not more than 9.0 per cent of its weight, when dried to constant weight at 105°, Appendix 5.8.

SULPHATED ASH – Not more than 0.1 per cent, Appendix 3.2.7.

ASSAY – Carry out the method for the *determination of nitrogen, Method A*, Appendix 3.3.5, using 0.15 g and 7 ml of *nitrogen-free sulphuric acid*. Each ml of *0.1N sulphuric acid* is equivalent to 0.00639 g of $C_6H_9N_3O_2,HCl$.

Holmium Oxide : $Ho_2O_3 = 377.86$

DESCRIPTION – A yellow solid.

SOLUBILITY – Practically insoluble in *water*.

Holmium Perchlorate Solution

A 5 per cent w/v solution of *holmium oxide* in *1.4 M perchloric acid*.

Hydrazine Hydrate : $NH_2.NH_2,H_2O = 50.06$

DESCRIPTION – Clear, colourless liquid with an ammoniacal odour.

SOLUBILITY – Miscible with *water*.

WT. PER ML – 1.03 g, Appendix 5.19.

Hydrazine Sulphate : $NH_2.NH_2,H_2SO_4 = 130.12$

Contains not less than 99.0 per cent of $N_2H_6SO_4$.

DESCRIPTION – White, crystalline powder.

SOLUBILITY – Freely soluble in *water*; practically insoluble in *alcohol*.

MELTING POINT – About 254°, Appendix 5.11.

CHLORIDE – 1 g complies with the *limit test for chlorides*, Appendix 3.2.2.

IRON – 1 g complies with the *limit test for iron*, Appendix 3.2.5.

SULPHATED ASH – Not more than 0.05 per cent, Appendix 3.2.7.

ASSAY – Weigh accurately about 0.1 g and dissolve in 20 ml of *water*. Add 3 g of *sodium bicarbonate* and titrate with *0.1N iodine*, using *starch solution* as indicator. Each ml of *0.1N iodine* is equivalent to 0.003253 g of $N_2H_6SO_4$.

Hydriodic Acid : HI = 127.91

Constant-boiling hydriodic acid contains 55.0 per cent w/w of HI (limits, 54.0 to 56.0).

DESCRIPTION – Almost colourless liquid when freshly made, but rapidly becoming yellow to brown owing to the liberation of iodine.

SOLUBILITY – Miscible in all proportions with *water* and with *alcohol*.

BOILING POINT – About 127°, Appendix 5.3.

WT. PER ML – At 20°, about 1.7 g, Appendix 5.19.

CHLORIDE AND BROMIDE – To 0.2 ml add 15 ml of *water*, 50 mg of *sodium sulphate*, 5 ml of *dilute ammonia solution* and 20 ml of *0.1N silver nitrate*, shake and filter; to the filtrate add 10 ml of *dilute nitric acid*. The opalescence produced is not greater than the standard opalescence obtained in the *limit test for chlorides*, Appendix 3.2.2.

SULPHATE – Dilute 1 ml with 50 ml of *water* and add 1 ml of *barium chloride solution*. The turbidity produced should not be greater than the standard opalescence obtained in the *limit test for sulphates*, Appendix 3.2.8.

NON-VOLATILE MATTER – When evaporated on a water-bath, and dried to constant weight at 105°, leaves not more than 0.5 per cent w/w of residue.

ASSAY – Weigh accurately about 0.6 g into a stoppered flask containing about 10 ml of *water*, dilute with 25 ml of *water* and titrate the free iodine with *0.1N sodium thio-*

TABLE 2

Size No.	Kinematic Viscosity Range (Centistokes)	Volume Bulb C (ml) (±5%)	Inside Diameter of Tube N (mm)	Inside Diameter of Tube R (mm) (±2%)
1	3.5* to 10	0.64	5.6	2.8 to 3.2
1A	5 to 30	0.84	5.6	2.8 to 3.2
2	20 to 100	1.15	5.6	2.8 to 3.2
2A	60 to 300	1.51	5.6	2.8 to 3.2
3	200 to 1100	2.06	5.6	3.7 to 4.3
3A	600 to 3000	2.74	5.6	4.6 to 5.4
4	2000 to 10,000	3.70	5.6	4.6 to 5.4
4A	6000 to 30,000	4.97	5.6	5.6 to 6.4
5	20,000 to 100,000	6.76	5.6	6.8 to 7.5

350 minimum flow time; 200 minimum flow time for all other sizes

any time while the flow time is being measured, the determination must be repeated.

Calculate the kinematic viscosity in centistokes (V) from the equation:

$$v = Ct.$$

where

t = time in seconds for the meniscus to fall from E to F

C = the constant of the viscometer, determined by observations on a liquid of known viscosity.

Method C : (Using the Rotating Viscometer)

The rotating viscometer measures the shearing forces in a liquid medium placed between two coaxial cylinders one of which is driven by a motor and the other is caused to revolve by the rotation of the first. Under these conditions, the viscosity becomes a measurement of the angle of deflection of the cylinder caused to revolve, expressed in newton metres.

Method—Operate the Rotating Viscometer in accordance with the manufacturer's instructions and carry out the determination of viscosity of the liquid being examined, at the temperature and angular velocity or shear rate specified in the individual monograph.

Calculate the dynamic viscosity (n) in centipoises.

5.19 WEIGHT PER MILLILITRE AND SPECIFIC GRAVITY

Weight per Millilitre

The weight per millilitre of a liquid is the weight in g of 1 ml of a liquid when weighed in air at 25°, unless otherwise specified.

Method : Select a thoroughly clean and dry pycnometer. Calibrate the pycnometer by filling it with recently boiled and cooled *water* at 25° and weighing the contents. Assuming that the weight of 1 ml of *water* at 25° when weighed in air of density 0.0012 g per ml. is 0.99602 g, calculate the capacity of the pycnometer. (Ordinary deviations in the density of air from the value given do not affect the result of a determination significantly). Adjust the temperature of the substance to be examined, to about 20° and fill the pycnometer with it. Adjust the temperature of the filled pycnometer to 25°, remove any excess of the substance and weigh. Subtract the tare weight of the pycnometer from the filled weight of the pycnometer. Determine the weight per millilitre by dividing the weight in air, expressed in g, of the quantity of liquid which fills the pycnometer at the specified temperature, by the capacity expressed in ml, of the pycnometer at the same temperature.

Specific Gravity

The specific gravity of a liquid is the weight of a given volume of the liquid at 25° (unless otherwise specified) compared with the weight of an equal volume of *water* at the same temperature, all weighings being taken in air.

Method : Proceed as described under **Wt. per ml.** Obtain the specific gravity of the liquid by dividing the weight of the liquid contained in the pycnometer by the weight of *water* contained, both determined at 25° unless otherwise directed in the individual monograph.

12831-c

Hydrazine Sulphate.

$H_6N_2O_4S = 130.1$

CAS — 302-01-2 (hydrazine); 10034-93-2 (sulphate).

Crystals. **Soluble** 1 in about 33 of water, freely soluble in hot water; practically **insoluble** in alcohol. A 0.2M solution in water has a pH of 1.3.

Hydrazine sulphate is employed in various industrial processes. It is used in the preparation of hydrazine hydrate which is applied after a solution of platinic chloride for corneal tattooing (see Chloroplatinic Acid, p.1693).

An account of the successful treatment of industrial hydrazine poisoning with pyridoxine.— J. K. Kirklin *et al.*, *New Engl. J. Med.*, 1976, *294*, 938.

A report of fatal choroidal melanoma in a worker who had been exposed to hydrazine for 6 years.— D. M. Albert and C. A. Puliafito (letter), *New Engl. J. Med.*, 1977, *296*, 634.

The use of hydrazine sulphate by a laboratory worker was associated with the development of a syndrome similar to systemic lupus erythematosus.— P. J. Durant and R. A. Harris (letter), *New Engl. J. Med.*, 1980, *303*, 584.

A discussion of hydrazine sulphate as an antineoplastic agent.— W. Regelson, *J. Am. med. Ass.*, 1980, *243*, 337.

12832-k

Hydrogen Sulphide. Sulphuretted Hydrogen.

$H_2S = 34.08$.

CAS — 7783-06-4.

A colourless inflammable gas with a characteristic odour; the intensity of the smell gives no indication of concentration.

Adverse Effects. Hydrogen sulphide poisoning is a common industrial hazard and is encountered in such places as chemical works, mines, sewage works, and stores of decomposing protein; concentrations of 0.1 to 0.2% in the atmosphere may be fatal in a few minutes. Pulmonary irritation, oedema, and respiratory failure usually occur in acute poisoning; prolonged exposure to low concentrations may give rise to severe conjunctivitis with photophobia and corneal opacity, irritation of the respiratory tract, rhinitis, bronchitis, stomatitis, pharyngitis, digestive disturbances, headache, lassitude, and skin rashes. There are some similarities to poisoning with cyanides.

A discussion of poisoning by hydrogen sulphide.— *Lancet*, 1978, *1*, 28. Comments.— A. Downie (letter), *ibid.*, 219; C. H. B. Binns (letter), *ibid.*, 501; A. Downie (letter), *ibid.*

Concentrations of about 200 ppm caused irritation of the respiratory tract and, on prolonged exposure, pulmonary oedema. Toxicity to the CNS could occur suddenly at concentrations in excess of 500 ppm and immediate death might follow concentrations in excess of 1000 ppm. Irritation to the eyes occurred at concentrations of less than 50 ppm.— *Methods for the Detection of Toxic Substances in Air, Hydrogen Sulphide*, London, HM Stationery Office, 1969.

Further references: W. W. Burnett *et al.*, *Can. med. Ass. J.*, 1977, *117*, 1277; R. P. Smith (letter), *ibid.*, 1978, *118*, 775; W. W. Burnett and E. G. King (letter), *ibid.*, 776; *J. Am. med. Ass.*, 1978, *239*, 1374.

Treatment of Adverse Effects. After exposure to hydrogen sulphide place the patient in fresh air, give inhalations of oxygen and, if necessary, assist the respiration. Antibiotics may be necessary if pulmonary infection occurs. The conjunctival sacs should be carefully washed out if eye irritation is severe.

In severe poisoning, amyl nitrite inhalation and sodium nitrite by intravenous injection have been suggested.

A brief review of the management of sulphide poisoning.— R. P. Smith and R. E. Gosselin, *A. Rev. Pharmac. & Toxic.*, 1976, *16*, 189.

The successful treatment of a 47-year-old man with severe hydrogen sulphide poisoning using oxygen, amyl nitrite inhalations for 30 seconds out of each minute for 5 minutes, and then sodium nitrite 300 mg intravenously for 3 minutes. Treatment was aimed at producing methaemoglobinaemia to inactivate the sulphide. In addition he received sodium thiosulphate 12.5 g by intravenous injection.— R. J. Stine *et al.*, *Ann. intern. Med.*, 1976, *85*, 756.

Further references: R. P. Smith and R. E. Gosselin, *J. occup. Med.*, 1979, *21*, 93.

Uses. Hydrogen sulphide is widely employed in many industrial processes.

12833-a

Hydroxyestrone Diacetate. 16α-Hydroxyoestrone Diacetate. 3,16α-Dihydroxyestra-1,3,5(10)-trien-17-one diacetate.

$C_{22}H_{26}O_5 = 370.4$.

CAS — 566-76-7 (hydroxyestrone); 1247-71-8 (diacetate).

Hydroxyestrone diacetate is a derivative of oestrone. It is claimed to have minimal systemic oestrogenic effects when given by mouth but to retain effects on the vaginal mucosa. It is used in the treatment of vaginitis and associated disorders.

Proprietary Names
Colpoginon *(Boizot, Spain)*; Colpogynon *(Laboratories de l'Hepatrol, Switz.)*; Colpormon *(Millet, Arg.; Anphar-Rolland, Fr.)*.

12834-t

Hydroxyethylpromethazine Chloride.

(2-Hydroxyethyl)dimethyl[1-methyl-2-(phenothiazin-10-yl)ethyl]ammonium chloride.

$C_{19}H_{25}ClN_2OS = 364.9$.

CAS — 7647-63-4 (hydroxyethylpromethazine); 2090-54-2 (chloride).

Hydroxyethylpromethazine chloride is an antihistamine.

Proprietary Names
Aprobit *(Recip, Swed.)*.

12835-x

Hydroxymethylnicotinamide. Nicotinylmethylamide; *N*-Hydroxymethylnicotinamide. *N*-Hydroxymethylpyridine-3-carboxamide.

$C_7H_8N_2O_2 = 152.2$.

CAS — 3569-99-1.

Crystals. M.p. 141° to 142°. Sparingly **soluble** in water and alcohol; freely soluble in hot water and alcohol.

Hydroxymethylnicotinamide is a choleretic and has been used in the treatment of various disorders of the gall-bladder.

Proprietary Names
Bilamid *(Cilag, Ger.; Bracco, Ital.; Cilag-Chemie, Switz.)*; Bilamide *(Cilag-Chemie, Belg.)*; Biloide *(Labatec-Pharma, Switz.)*.

12836-r

5-Hydroxytryptophan. 5-HTP; Ro-0783/B. 2-Amino-3-(5-hydroxy-1*H*-indol-3-yl)propionic acid.

$C_{11}H_{12}N_2O_3 = 220.2$.

CAS — 56-69-9.

NOTE. The form of 5-hydroxytryptophan used clinically is generally the L-form.

5-Hydroxytryptophan is a precursor of serotonin (see p.1753) and has been used clinically in attempts to treat disorders believed to be associated with serotonin deficiency.

Changes in mood, mostly elevation, were observed in 7 neurological patients without affective disorders and 1 healthy subject given L-5-hydroxytryptophan 100 to 300 mg by intravenous infusion in sodium chloride injection. Carbidopa was also given to reduce the severity of vomiting which always occurred 30 to 90 minutes after infusion and to increase the amount of L-5-hydroxytryptophan entering the brain. Neurotoxicity occurred with doses of 200 mg and above and included dilatation of the pupil, hyperreflexia, ataxia, and dysarthria. There was some similarity to the effects of a cohol.— M. Trimble *et al.* (letter), *Lancet*, 1975, *1*, 583. See also M. H. Greenwood *et al.*, *Br. J. clin. Pharmac.*, 1975, *2*, 165.

Severe insomnia in a 33-year-old woman following a road accident responded to 4 consecutive nightly doses of L-5-hydroxytryptophan totalling 3 g.— M. Webb and J. G. Kirker (letter), *Lancet*, 1981, *1*, 1365.

Manganese poisoning. A beneficial response to DL-5-hydroxytryptophan, up to 3 g daily, was achieved in a patient in whom the symptoms of manganese poisoning failed to respond to levodopa.— I. Mena *et al.*, *New Engl. J. Med.*, 1970, *282*, 5.

Mental disorders. Of 107 patients with endogenous depression given L-5-hydroxytryptophan daily in divided doses by mouth for at least 5 weeks, the majority rapidly obtained a beneficial response.— I. Sano, *Münch. med. Wschr.*, 1972, *114*, 1713, per *J. Am. med. Ass.*, 1972, *222*, 1085. Further studies in depression: N. S. Kline *et al.*, *Am. J. Psychiat.*, 1964, *121*, 379, per *Int. pharm. Abstr.*, 1965, *2*, 918; T. Persson and B.-E. Roos (letter), *Lancet*, 1967, *2*, 987; G. d'Elia *et al.*, *Acta psychiat. scand.*, 1978, *57*, 239; L. J. van Hiele, *Neuropsychobiology*, 1980, *6*, 230.

After oral administration of L-5-hydroxytryptophan with a peripheral decarboxylase inhibitor, mild to moderate improvement was obtained in 6 of 7 chronic undifferentiated schizophrenic patients who were resistant to phenothiazines. Of 4 chronic paranoid schizophrenic patients who were resistant to phenothiazines 2 became worse after treatment with 5-hydroxytryptophan and 1 improved. Some schizophrenic patients might have an abnormality in serotonin metabolism.— R. J. Wyatt *et al.*, *Science*, 1972, *177*, 1124.

Further studies in schizophrenia: V. Zarcone *et al.*, *Archs gen. Psychiat.*, 1973, *28*, 843; R. J. Wyatt *et al.*, *ibid.*, *29*, 597.

Myoclonus. Comment on the use of the investigational drug L-5-hydroxytryptophan in the treatment of myoclonus and the view that in general its use should be discouraged. L-5-Hydroxytryptophan is usually effective in posthypoxic intention myoclonus, a rare condition, but may exacerbate some other myoclonic syndromes. Significant adverse effects, especially gastro-intestinal disturbances, are almost universal, even when given with a peripheral decarboxylase inhibitor such as carbidopa.— R. R. Young, *J. Am. med. Ass.*, 1980, *243*, 1569.

L-5-Hydroxytryptophan with carbidopa was administered to 23 patients with myoclonus and 16 patients with other neurological disorders. Following administration by mouth of maximum doses of 0.4 to 2 g daily with carbidopa 100 to 300 mg daily more than 50% improvement was obtained in 11 of 18 patients with intention myoclonus due to anoxia or other brain damage; only 1 patient obtained no improvement and in 3 it was 90% or more, some patients derived sustained benefit for more than 3 years. No benefit was obtained by 2 patients with athetotic cerebral palsy, 2 with multiple sclerosis, 2 with essential tremor, 4 with cerebellar intention tremor, 1 with infantile spasms, 2 with dystonia musculorum deformans, 2 with central pain syndromes, or 3 with idiopathic epilepsy; some benefit was obtained in 1 patient with myoclonus epilepsy and in 1 of 2 patients with familial essential myoclonus. Side-effects included anorexia, nausea, diarrhoea, and occasional vomiting and were reduced by prochlorperazine or trimethobenzamide and diphenoxylate; prior administration of carbidopa for 1 or 2 days before therapy also reduced the gastro-intestinal side-effects. During the first week of therapy 3 patients developed dyspnoea followed by hyperventilation and lightheadedness, with fainting in 1; pulmonary function tests remained normal. Varying degrees of mental stimulation occurred in 10 patients; these were reversible on dosage reduction and frequently disappeared or diminished after 4 to 6 weeks without reduction, but 2 patients required concurrent administration of perphenazine to maintain their antimyoclonic dosage. Other side-effects included mydriasis, blurring of vision, abdominal pain, and bradycardia.— M. H. Van Woert *et al.*, *New Engl. J. Med.*, 1977, *296*, 70. Comment.— T. L. Munsat, *ibid.*, 101.

Studies suggesting that the treatment of intention myoclonus with L-5-hydroxytryptophan and carbidopa in a 70-year-old man unmasked an abnormality in his ability to metabolise kynurenine and resulted in the development of a scleroderma-like illness.— E. M. Sternberg *et al.*, *New Engl. J. Med.*, 1980, *303*, 782.

Further references: D. Chadwick *et al.*, *Lancet*, 1975, *2*, 434; J. DeLéan and J. C. Richardson (letter), *ibid.*, 870; J. H. Growdon *et al.*, *Neurology, Minneap.*, 1976, *26*, 1135; W. M. Carroll and P. J. Walsh, *Br. med. J.*,

rastis canadensis L.. and canadine. Syn- ydrastines: Hope *et et al., ibid.* **1934**, rm. *Bull.* **27**, 1947 *iron Letters* **22**, 619 Haworth, Pinder, *J.* .. *Nature* **165**, 529 n. **293**, 121 (1960). *Letters* **1963**, 859; n. **29**, 2328 (1964); 969). Biosynthesis 963).

$[\alpha]_D^{20} - 50°$ (c = 218, 238, 298, 316 7.8. Freely sol in ne salts hydrolyze

R. Paech, M. V. **vol. IV** (Springer- 116°. $[\alpha]_D^{17}$ -127° cohol; slightly sol 5% soln): 4.2

as ... rine hemo-

vdro-6-methyl-1,3- -6,7-methylenedi- line. $C_{11}H_{13}NO_3$: 6.76%, O 23.16%. Will, *Ber.* **20**, 88 t. **241,136** (1910). yman, Remfry, *J.* . *J. Appl. Chem.* topiperonylamine 13): Rosenmund, m safrole: Kind- Structure study

ly sol in alcohol. l in cold, moder- alcohol are yel- organic solvents Dobbie, Tinkl-

diotonic; uterine

ge root; yellow ned rhizome and aceae, contg not t. North Amer- berine; canadine.

N_2; mol H_2 epn from m. Soc. **76**, 3914 *Inorganic Chem-*

istry vol. 1, G. Brauer, Ed. (Academic Press, New York, 1963) pp 469-472. Toxicity data: Witkin, *Arch. Ind. Health* **13**, 34 (1956). Toxicology study: Back, Thomas, *Ann. Rev. Pharmacol.* **10**, 395 (1970). Review of carcinogenicity studies: *IARC Monographs* **4**, 127-136 (1974); of toxicology: R. von Burg, T. Stout, *J. Appl. Toxicol.* **11**, 447-450 (1991). Books: L. F. Audrieth, B. A. Ogg, *The Chemistry of Hydrazine* (Wiley, New York, 1951); C. C. Clark, *Hydrazine* (Mathieson Chem., Baltimore, 1953). *Reviews:* Troyan, *Ind. Eng. Chem.* **45**, 2608-2612 (1953); Zimmer, *Chem. Zig.* **79**, 599-605 (1955); Hudson *et al.*, "Hydrazine" in *Mellor's* vol. VIII, suppl. II, *Nitrogen* (Part 2), 69-114 (1967); Jones in *Comprehensive Inorganic Chemistry* vol. 2, J. C. Bailar, Jr. *et al.*, Eds. (Pergamon Press, Oxford, 1973) p 250-265; H. W. Schiessl in Kirk-Othmer *Encyclopedia of Chemical Technology* vol. 13 (John Wiley & Sons, New York, 4th ed., 1995) pp 560-606.

Colorless oily liq, fuming in air. Penetrating odor resembling that of ammonia. Burns with violet flame. Explodes during distn if traces of air are present, also affected by uv and metal ion catalysts. Can be stored for years if sealed in glass and kept in a cool, dark place. Flash and fire pt 126°F (52°C). Contracts on freezing. d_4^{-5} 1.146; d_4^0 1.0253; d_4^{15} 1.024; d_4^{15} 1.011; d_4^{25} 1.0036; d_4^{35} 0.9955. One gallon of commercial product weighs 8.38 lbs. mp 2.0°, bp_{760} 113.5°; bp_{71} 56°; $bp_{5\ mm}$ 170°; $bp_{10\ mm}$ 200°; $bp_{20\ mm}$ 236°. $n_D^{22.5}$ 1.46979; n_D^{25} 1.46444. Dipole moment 1.83-1.90. Dielectric constant (25°): 51.7. Latent heat of fusion (mp): 3.025 kcal/mole; latent heat of vaporization (bp): 9760 kcal/mole (calc). Crit temp 380°, crit pressure 14 atm. Diacidic base. pK_1 (25°): ~6.05. Forms salts with inorganic acids. Highly polar solvent. Powerful reducing agent. Dissolves many inorganic substances. Misc with water, methyl, ethyl, propyl, isobutyl alcohols. Forms an azeotropic mixture with water, bp_{760} 120.3°, which contains 55 mole-% (68.5 weight-%) N_2H_4. LD_{50} in mice (mg/kg): 57 i.v.; 59 orally (Witkin).

Dihydrochloride, $H_6N_2.2HCl$, white crystalline powder, mp 198°, d 1.42. Freely sol in water, slightly in alcohol.

Caution: Potential symptoms of overexposure to hydrazine are irritation of eyes, nose and throat; temporary blindness; dizziness, nausea; dermatitis; burns skin and eyes. *See NIOSH Pocket Guide to Chemical Hazards* (DHHS NIOSH 90-117, 1990) p 124. *See also* Patty's *Industrial Hygiene and Toxicology*: vol. **2E**, G. D. Clayton, F. E. Clayton, Eds. (John Wiley & Sons, Inc., New York, 4th ed., 1994) pp 3435-3441. Hydrazine may reasonably be anticipated to be a carcinogen. *Seventh Annual Report on Carcinogens* (PB95-109781, 1994) p 231.

USE: Chemical intermediate in manuf of agricultural chemicals, spandex fibers and antioxidants. Reducing agent; organic hydrazine derivs; rocket fuel. Dihydrochloride as chlorine scavenger for HCl gas streams.

4810. Hydrazine Hydrate. H_6N_2O; mol wt 50.06. H 12.08%, N 55.96%, O 31.96%. $H_2NNH_2.H_2O$. Prepd from hydrazine sulfate by the action of NaOH, followed by distn under nitrogen.

Fuming refractive liquid, faint characteristic odor. *Violent poison! Causes delayed eye irritation.* d^{21} 1.03. mp −51.7° or below −65° (two eutectics). bp_{740} 118-119°; bp_{36} 47°. n_D^{20} 1.42842. Strong base, very corrosive, attacks glass, rubber, cork, but not stainless V_2A steel or Allegheny stainless 304 and 347. Molybdenum steels such as Allegheny stainless 316 should not be used. Very powerful reducing agent. Miscible with water and alcohol. Insol in chloroform and ether.

Mixture with methanol, *C-Stuff.*

USE: Reducing agent, solvent for inorganic materials. Manuf "Helman" catalyst, consisting of 80% hydrazine hydrate, 19.5% ethanol, 0.5 to 0.05% copper, used to dec hydrogen peroxide in V-2 type rockets. Mixture with methanol as propellant for rocket engines.

4811. Hydrazine Sulfate. Hydrazinium sulfate; hydrazonium sulfate. $H_6N_2O_4S$; mol wt 130.12. H 4.65%, N 21.53%, O 24.18%, S 24.64%. $H_2NNH_2.H_2SO_4$. Prepd by Raschig synthesis $2NH_3$,aq - [$Ca(OCl)_2$/Na_2CO_3 colloid] and treatment with H_2SO_4. Starch, glue, or gelatin are used as colloids, and sodium hypochlorite may be used instead of bleaching powder. Adams, Brown, *Org. Syn.* **2**, 37 (1922).

Audrieth, Nickles, *Inorg. Syn.* **1**, 90 (1939). Industrial prepn by the action of sodium hypochlorite on urea in the presence of NaOH: *B.I.O.S. Final Report* **369**; Moncrieff, *Manuf. Chem.* **18**, 177 (1947). Revised lab procedures: Pfeiffer, Simons, *Ber.* **80**, 127 (1947); Adams, Brown, *Org. Syn.* coll. vol. **1**, 2nd ed. (1941), p 309. Crystal structure: Nitta *et al.*, *Acta Cryst.* **4**, 289 (1951); Jönsson, Hamilton, *ibid.* **26B**, 536 (1970). Review of activity and clinical studies in cancer cachexia: J. Gold, *Nutr. Cancer* **9**, 59-66 (1987).

Orthorhombic crystals. Glass-like plates or prisms. d 1.378; Curtis, Jay, *J. Prakt. Chem.* **39**, 39 (1889); d^7 2.016. mp 254°. Sol in about 33 parts water; freely sol in hot water. Insol in alcohol. pH of 0.2 molar aq soln 1.3.

Note: This substance may reasonably be anticipated to be a carcinogen: *Seventh Annual Report on Carcinogens* (PB95-109781, 1994) p 231.

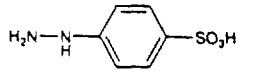
USE: In the gravimetric estimation of nickel, cobalt and cadmium; in the refining of rare metals; as antioxidant in soldering flux for light metals; as reducing agent in the analysis of minerals and slags; in separating polonium from tellurium; in tests for blood; for destroying fungi and molds; in the prepn of hydrazine hydrate.

4812. Hydrazine Tartrate. Hydrazine acid tartrate; hydrazine hydrogen tartrate; hydrazine bitartrate. $C_4H_{10}N_2O_6$; mol wt 182.13. C 26.38%, H 5.53%, N 15.38%, O 52.71%. $H_2NNH_2.C_4H_6O_6$.

Crystals, mp 182-183°. $[\alpha]_D^{20}$ +22.5°. Soly in water at 0° about 6 g/100 ml. pH of a satd aq soln 3.6.

USE: In chemical deposition of metals (silvering mirrors, etc.): Owen, U.S. pat. **2,801,935** (1957 to Merck & Co.).

4813. 4-Hydrazinobenzenesulfonic Acid. *p*-Sulfophenylhydrazine; phenylhydrazine-*p*-sulfonic acid. $C_6H_8N_2O_3S$; mol wt 188.21. C 38.29%, H 4.28%, N 14.88%, O 25.50%, S 17.04%. Prepn by sulfonation of phenylhydrazine: L. Claisen, P. Roosen, *Ann.* **278**, 296 (1894); by the reduction of *p*-diazobenzenesulfonic acid: Th. Zincke, A. Kuchenbecker, *Ann.* **330**, 1 (1903); L. V. Lazeeva *et al.*, USSR pat. **1,057,493** (1983 to Tambov Pigment). *C.A.* **100**, 138755q (1984). Used in resoln of 2-pyrazoline cmpds: M. Mukai *et al.*, *Can. J. Chem.* **57**, 360 (1979); in isoln of volatile ketones: W. Treibs, H. Röhnert, *Ber.* **84**, 433 (1951); in analysis of trace amounts of selenium: T. Kawashima *et al.*, *Anal. Chim. Acta* **49**, 443 (1970); *eidem, ibid.* **89**, 65 (1977).



Needles from water, mp 286°. Slightly sol in water, alcohol.

4814. 2-Hydrazinoethanol. 2-Hydroxyethylhydrazine; β-hydroxyethylhydrazine; Omaflora. $C_2H_8N_2O$; mol wt 76.10. C 31.57%, H 10.60%, N 36.81%, O 21.02%. $HOCH_2CH_2NHNH_2$. Prepn from hydrazine monohydrate and 2-chloroethanol: Gansser, Rumf, *Helv. Chim. Acta* **36**, 1423 (1953); from hydrazine monohydrate and ethylene oxide: Gever, O'Keefe, U.S. pat. **2,660,607** (1953 to Eaton Labs.); from hydrazine and ethylene oxide: Brit. pat. **776,113** (1957 to Olin Mathieson).

Colorless, slightly viscous liquid. d 1.11. One gallon weighs 9.26 lbs. mp −70°. $bp_{17.5}$ 110-130°; bp_{25} 145-153°. Flash pt 224°F (106°C). Misc with water. Sol in the lower alcohols. Slightly sol in ether.

USE: Plant growth regulant.

4815. Hydrazoic Acid. Hydrogen azide; hydronitric acid; triazoic acid; stickstoffwasserstoffsäure (German). HN_3; mol wt 43.03. H 2.34%, N 97.66%. Produced by the action of sulfuric acid on sodium azide: L. F. Audrieth, C. F. Gibbs, *Inorg. Syn.* **1**, 77 (1939); using stearic acid: Günther, Meyer, *Z. Elektrochem.* **41**, 541 (1935). Prepn of water and ether solns of hydrazoic acid: W. S. Frost *et al.*, *J. Am. Chem. Soc.* **55**, 3516 (1933); L. F. Audrieth, C. F. Gibbs, *loc. cit.*; P. W. Schenk in *Handbook of Preparative Inorganic Chemistry* vol. **1**, G. Brauer, Ed. (Academic Press, New York, 2nd ed., 1963) pp 472-474. GC determn: J. M. Zehner, R.A. Simonaitis, *J. Chrom. Sci.* **14**, 493 (1976). Toxicity study: Grahan Review of toxicol Patty's *Industrial* Clayton, F. E. C York, 1981) pp 2 *Comprehensive Tre istry* vol. **VIII**, su Jones in *Compreh* Bailar Jr. *et al.*, E 276-293.

Mobile liquid. l *plosive!* mp −8C (mg/kg): 21.5 i.p. *Caution: Acute* fall in blood pressu hypotension, weakr

USE: Industrially detonators.

4816. Hydrin *ene]-1,1',3,3'-(2H,2' 1,1',3,3'-tetrone;* r 322.27. C 67.09%, tion of potassium c *J. Org. Chem.* **23**, 1 tion of ninhydrin w *Chem.* **211**, 907 (19

Dihydrate, prism- reddish-brown at 2C hot water; sol in M aq Na_2CO_3 solns (de blue color). Can b the addn of acid. blue color with amir

USE: Reagent for acids and similar co

4817. Hydriodi water. Marketed ir 47%, d 1.5; 10%, d iodide gas in water sulfide according to Frykholm, *Inorg. Sy* Iodide.

Colorless when fre or brown on exposu can be prevented by phorous acid (H_3PO_3 for some time are us be regenerated with Jr., *Inorg. Syn.* **2**, 21(*air, preferably not abc* Dissolves iodine. bp_{760} 127°, d 1.70, c acid, attacks natural

Caution: Strong ir

USE: Reducing ag maceuticals, disinfect analytical purposes, s

THERAP CAT: Expec

4818. Hydroben phenylethyleneglycol. H 6.59%, O 14.93%. Forst, Zincke, *Ann.* *Chem. Soc.* **91**, 1390 *Soc.* **51**, 2163 (1929); C. Heath, Boston, 1 Improved method for mer: Collet, *Synthesis*

HYDRAZINE SULFATE

"...Since hydrazine sulfate provided relief of a wide spectrum of cancer symptoms, it may be recommended for patients with end-stage cancer."

"...virtually no significant untoward side effects..."

Articles
How to
Contact Us

GENERAL INFORMATION

Hydrazine sulfate is an anti-cachexia drug which acts to reverse the metabolic processes of debilitation and weight loss in cancer and secondarily acts to stabilize or regress tumors. Hydrazine sulfate is a monoamine oxidase (MAO) inhibitor and is incompatible with tranquilizers, barbiturates, alcohol and other central nervous system depressants. Foods high in tyramine, such as aged cheeses and fermented products, are also incompatible with MAO inhibitors. The use of tranquilizers, barbiturates and/or alcoholic beverages with hydrazine sulfate destroys the efficacy of this drug and increases patient morbidity.

The U.S. National Cancer Institute (NCI)-published studies of hydrazine sulfate (Journal of Clinical Oncology, June 1994), reported as negative, denied the use of tranquilizers, with the exception of the short-term use of prochlorperazine (Compazine). However, under pressure of an investigation of the NCI studies by the U.S. General Accounting Office ordered by Congress, the NCI in a subsequently published paper (Journal of Clinical Oncology, June 1995) admitted to the widespread use of both benzodiazepine and phenothiazine tranquilizers, which are incompatible with MAO inhibitors, in 94% of all study patients. Moreover, approximately half of these patients were given these tranquilizers on a long-term basis, and some on a continual basis. It was further admitted by the NCI that concomitant drug use (such as tranquilizers, alcohol, barbiturates, etc.) was not computerized and patient

records of such drug use were "incomplete."

There is an abundance of published, positive, peer-reviewed studies on hydrazine sulfate in the medical literature. (Abstracts of some of these published studies are given on the following pages.) These data emanate from major cancer centers both from the United States (randomized, double-blind, placebo-controlled studies and single-arm studies) and Russia (large-scale, multicentric Phase II-equivalent studies). These data indicate the therapeutic action of hydrazine sulfate to extend to all types of tumors.

Hydrazine sulfate has been demonstrated to produce only few and transient side effects. There have been no instances of bone-marrow, heart, lung, kidney or immune system toxicity, or death, reported. Hydrazine sulfate has never been demonstrated to be carcinogenic in humans.

For further information please have your HEALTH CARE PROFESSIONAL (no patients or individuals, please) call the institute.

COLLECTION OF ARTICLES | HOW TO CONTACT SCRI

A collection of articles on Hydrazine Sulfate has been available on this site since 23 October 1996.

General Information
How to Contact Us

ARTICLES

The following is a collection of articles based on published studies on Hydrazine Sulfate. You may view the abstract by clicking on the icon to the left. If the title of an article has no hyperlink, then that article is not present on this system (you may still view the abstract).


"Hydrazine Sulfate Influence on Nutritional Status and Survival in Non-Small-Cell Lung Cancer" [Journal of Clinical Oncology 8:9-15, 1990]


"Results of Clinical Evaluation of Hydrazine Sulfate" [VOPROSY ONKOLOGII 36:721-726, 1990]


"Altered Metabolism and Mortality in Patients With Colon Cancer Receiving Chemotherapy" [American Journal of the Medical Sciences 310:48-55, 1995]


"Influence of Hydrazine Sulfate on Abnormal Carbohydrate Metabolism in Cancer Patients with Weight Loss" [Cancer Research 44:857-861, 1984]


"Treatment of Primary Brain Tumors With Sehydrin [Hydrazine Sulfate]" [VOPROSY ONKOLOGII 40:332-336, 1994]


"Hydrazine Sulfate in Cancer Patients With Weight Loss: A Placebo-Controlled Clinical Experience" [Cancer 59:406-410, 1987]


"Anabolic Profiles in Late-Stage Cancer Patients Responsive to Hydrazine Sulfate" [Nutrition and Cancer 3:13-19, 1981]

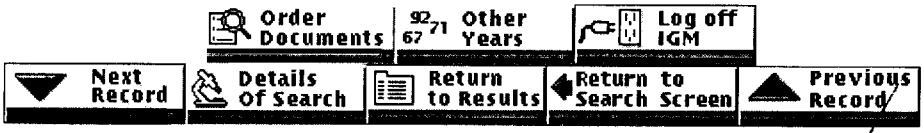

"Effect of Hydrazine Sulfate on Whole-body Protein Breakdown Measured by 14C-Lysine Metabolism in Lung Cancer Patients" [Lancet 2:241-244, 1987]


"Hydrazine Sulfate: A Current Perspective" [Nutrition and Cancer 9:59-66, 1987]


"Experience of the treatment with Sehydrin (Hydrazine Sulfate, HS) in the advanced cancer patients" [Investigative New Drugs 13:89-97, 1995]


"Use of Hydrazine Sulfate in Terminal and Preterminal Cancer Patients: Results of Investigational New Drug (IND) Study in 84 Evaluable Patients" [Oncology 32: 1-10, 1975]

National Library of Medicine: IGM Full Record Screen



TITLE: Use of hydrazine sulfate in terminal and preterminal cancer patients: results of investigational new drug (IND) study in 84 evaluable patients.

AUTHOR: Gold J

SOURCE: Oncology 1975;32(1):1-10

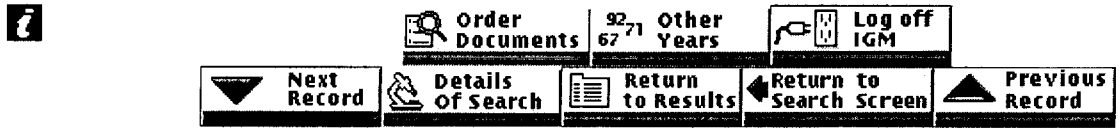
NLM CIT. ID: 76101548

ABSTRACT: In a series of 84 various evaluable disseminated cancer patients treated with hydrazine sulfate as a result of a pharmaceutical-sponsored investigational new drug (IND) study, it was found that 59/84 or 70% of the cases improved subjectively and 14/84 or 17% improved objectively. Subjective responses included increased appetite with either weight gain or cessation of weight loss, increase in strength and improved performance status and decrease in pain. Objective responses included measurable tumor regression, disappearance of or decrease in neoplastic-associated disorders and long-term (over 1 year) 'stabilized condition'. Of the overall 59 subjective improvements 25 (42%) had no concurrent or prior (within 3 months) anticancer therapy of any type. Of the 14 objective improvements 7 (50%) had no concurrent or prior anticancer therapy. Of the remaining cases in which there was either concurrent or prior anticancer therapy, improvements occurred only after the addition of hydrazine sulfate to the treatment regimen. Duration of improvement was variable, from temporary to long-term and continuing. Side effects were mild, comprising for the most part low incidences of extremity paresthesias, nausea, pruritis and drowsiness; there was no indication of bone marrow depression.

MAIN MESH SUBJECTS: Hydrazines/ADVERSE EFFECTS/PHARMACOLOGY/*THERAPEUTIC USE
Neoplasms/*DRUG THERAPY/METABOLISM

ADDITIONAL MESH SUBJECTS: Drug Evaluation
Gluconeogenesis/DRUG EFFECTS
Human

Paresthesia/CHEMICALLY INDUCED
Remission, Spontaneous
PUBLICATION TYPES: **JOURNAL ARTICLE**
LANGUAGE: **Eng**



National Library of Medicine: IGM Full Record Screen

TITLE: Hydrazine sulfate in cancer patients with weight loss. A placebo-controlled clinical experience.

AUTHOR: Chlebowski RT; Bulcavage L; Grosvenor M; Tsunokai R; Block JB; Heber D; Scrooc M; Chlebowski JS; Chi J; Oktay E; et al

SOURCE: Cancer 1987 Feb 1;59(3):406-10

NLM CIT. ID: 87077829

ABSTRACT: Hydrazine sulfate was evaluated using 24-hour dietary recalls and body weight determinations before and after 30 days of either placebo or hydrazine (60 mg, 3 times/d) oral administration in 101 heavily pretreated cancer patients with weight loss. After 1 month, 83% of hydrazine and only 53% of placebo patients completing repeat evaluation maintained or increased their weight (P less than 0.05). In addition, appetite improvement was more frequent in the hydrazine group (63% versus 25%, P less than 0.05). Although caloric intake was only slightly greater in hydrazine-treated patients, an increased caloric intake was more commonly associated with weight gain in patients receiving hydrazine compared with those receiving placebo (81% versus 53%, respectively). Hydrazine toxicity was mild, with 71% of patients reporting no toxic effects. Hydrazine sulfate circulatory levels were obtained from a subset of 14 patients who completed 30 days of treatment, with a single sample obtained in the morning at least 9 hours after the last dose. Mean maintenance hydrazine sulfate levels, determined using a spectrofluorometric assay, ranged from 0 to 89 ng/ml (mean 45 +/- 16 ng/ml). These data, which demonstrate an association between 1 month of hydrazine sulfate administration and body weight maintenance in patients with cancer, suggest future clinical trials of hydrazine sulfate are indicated to definitively assess its long-term impact on important clinical outcome parameters in defined cancer populations.

MAIN MESH SUBJECTS: Cachexia/*DRUG THERAPY/ETIOLOGY
Hydrazines/*THERAPEUTIC USE
Neoplasms/*COMPLICATIONS/DRUG THERAPY

Chapter 5

HYDRAZINE SULFATE

Hydrazine sulfate, a simple, off-the-shelf chemical, dramatically reverses cachexia (ka-KEK-si-a), the wasting-away process that kills two-thirds of all cancer patients. This inexpensive drug, with little or no side effects, also has a clinically documented antitumor action. It causes malignant tumors to stop growing, to reduce in size, and, in some cases, to disappear. A growing number of cancer patients diagnosed as terminal have experienced tumor stabilization and remission through hydrazine sulfate therapy.

About half of all patients who take hydrazine sulfate experience weight gain, restored appetite, extended survival time, and a significant reduction in pain and suffering. Many patients report an increase in vigor and strength and the disappearance of symptoms of the disease, along with feelings of well-being and optimism.

While hydrazine sulfate may not be a sure-fire cancer cure, large-scale clinical trials suggest that it affects every type of tumor at every stage. It can be administered either alone or in combination with cytotoxic chemotherapy or radiation to make the cancer more vulnerable to these standard forms of treatment.

Hydrazine sulfate is now undergoing Phase III trials sponsored by the National Cancer Institute. It is available to patients as a "compassionate IND [Investigational New Drug]," a designation conferred by the Food and Drug Administration on a case-by-case basis, so it is no longer, strictly speaking, an "unconventional therapy." Yet even though hundreds of patients across the country are using the drug, it is not widely discussed or disseminated among practicing physicians and its promise remains largely untapped twenty-four years after it was first proposed as an anticancer treatment by Dr. Joseph Gold. Meanwhile, hydrazine sulfate is widely available in the Com-

monwealth of Independent States (formerly the Soviet Union), where researchers have followed up on Gold's pioneering work with over ten years of investigation supporting the drug's effectiveness.

"We've gone from a red light to a yellow light, and hopefully will go to a green light," says Dr. Gold, director of the Syracuse Cancer Research Institute in Syracuse, New York, which he founded in 1966. Since his discovery in 1968 that hydrazine sulfate can prevent the wasting-away process in cancer patients and inhibit tumor growth, Gold has waged a courageous uphill battle to win acceptance for his nontoxic chemotherapy by the medical establishment.

The American Cancer Society put hydrazine sulfate on its Unproven Methods blacklist in 1976. It condemned and stigmatized the drug following a clinical trial on twenty-nine patients at Memorial Sloan-Kettering Cancer Center in New York. But it is now widely acknowledged that the Sloan-Kettering tests were botched.

When Dr. Gold made an unannounced visit to the hospital in 1974, he discovered, to his horror, that "many patients in the study were either being underdosed or overdosed. Some people who were beginning to show anticachexia response were suddenly being given 90 to 100 milligrams at one time. All this was in clear violation of the drug protocols and of our joint agreements," said Gold.[1] The study's protocol called for patients to receive 60 milligrams once a day for the first three days, twice a day for the next three days, and three times a day for the following six weeks. Therefore, some patients were getting a 67 percent overdose.

In a letter of protest to Sloan-Kettering,[2] Gold pointed out that some patients were receiving a massive, single dose of approximately 120 to 190 milligrams a day (instead of the usual two or three 60-milligram doses), "which quickly wiped out whatever good response they were beginning to show." The study was so poorly executed that it could never be published today, he maintains.

Nevertheless, the damage was done. The ACS's blacklisting of hydrazine sulfate caused Gold's funding to dry up and scared away other researchers from following up on his early papers.

But Gold refused to give up. In 1975, he did a study of the drug's effects on eighty-four advanced cancer patients. A total of 70 percent of them experienced weight gain (or the cessation of weight loss) and reduced pain. Only 17 percent showed tumor improvements. Meanwhile, Russian scientists at Leningrad's Petrov Research Institute were getting impressive results. In one study of forty-eight terminal cancer p[illegible]nts treated with hydrazine sulfate, 35 percent had tumor

stabilization or regression and 59 percent showed "subjective response" (ability to function normally, complete disappearance of marked reduction of pain, and so forth).

As a result of these and other favorable studies, the American Cancer Society announced in 1979 that it was removing hydrazine sulfate from its official blacklist. Only four other "unproven methods" that were once stigmatized on the ACS list as "quackery" have been removed from it. However, the ACS included hydrazine sulfate in the 1979 edition of the Unproven Methods list, and that edition continued to be circulated until 1982. Hydrazine sulfate was finally removed from the list the next time the list was revised, in July 1982.

Tim Hansen, now in his early twenties, of Minneapolis, Kansas, is one person grateful for the existence of hydrazine sulfate therapy. In August 1984, when he was eleven years old, Tim was diagnosed with three inoperable malignant tumors that were growing quickly in his brain. He was placed on radiation therapy, but his health steadily deteriorated until, by early 1985, his weight had dropped to fifty-five pounds. "The radiation harmed his mental functioning, and in January 1985 the surgeon told me that Tim had one week to live," says Gloria Hansen, Tim's mother.

In February, after reading a short item about hydrazine sulfate in *McCall's*, Gloria and her husband, Ray, got in touch with Dr. Gold and Tim was put on hydrazine sulfate therapy by his physicians in Kansas. By August, his weight was up to seventy-five pounds. By early 1987, two of Tim's tumors had completely vanished. In January 1990 a computerized axial tomograph (CAT scan) revealed further shrinkage of the remaining tumor, located in the base of the brain. Dr. Gold plans to keep Tim on the hydrazine sulfate protocol until the tumor is completely gone. Tim graduated from high school in 1990 and is now studying electronics at a trade school, getting A's and B's.

Dr. Gold first stumbled upon hydrazine sulfate's anticancer properties during his methodical quest for a specific type of therapy. Cancer has two principal devastating effects on the body. One is the invasion of the tumor into the vital organs, with the destruction of the organs' functions—the most common cause of cancer death in the public's mind. In reality, however, this accounts for only about 10 percent of the country's half-million annual cancer deaths.

The other devastating effect of cancer is cachexia, the terrible wasting away of the body, with its attendant weight loss and debilitation. In cancer, as in AIDS, patients succumb to the accompanying illness by which they would otherwise survive if not for the wasting syndrome

"In a sense, nobody ever dies of cancer," notes Dr. Harold Dvorak, chief of pathology at Beth Israel Hospital in Boston. "They die of something else—pneumonia, failure of one or another organs. Cachexia accelerates that process of infection and the building-up of metabolic poisons. It causes death a lot faster than the tumor would, were it not for the cachexia."[4]

Halting the wasting syndrome instead of directly attacking the cancer cells with poison was Dr. Gold's plan of attack. As he explains, "Each of these processes [the tumor invasion of vital organs and cachexia] has its own metabolic machinery, each is amenable to its own therapy, and each is to some degree functionally interdependent on the other. In the interest of treating the totality of malignant disease, each of these processes warrants intervention. Such an approach, dealing with *both* major underpinnings of the cancerous process—mitogenic and metabolic—affords the greatest promise for eliciting long-term, symptom-free survival and the potential for disease eradication."[5]

But what causes cachexia? Cancer cells gobble up sugar ten to fifteen times more than normal cells do. The sugar consumed by the cancer cells is generated mainly from the liver, which converts lactic acid into glucose. (Normal cells are far more efficient users of glucose, which they derive from the food we eat, not from lactic acid.) When cancer cells use sugar (glucose) as fuel, they only partially metabolize it. Lactic acid—the waste product of this incomplete combustion—spills into the blood and is taken up by the liver. The liver then recycles the lactic acid (and other breakdown products) back into glucose, and the sugar is consumed in ever-increasing amounts by voracious cancer cells. The result is a vicious cycle, what Dr. Gold calls a "sick relationship" between the liver and the cancer. The patient's healthy cells starve while the cancer cells grow vigorously. Some healthy cells even *dissolve* to feed the growing tumor.

To break this sick relationship, Gold reasoned, all he needed was to find a safe, nontoxic drug that inhibits *gluconeogenesis* (the liver's recycling of lactic acid back into glucose). In 1968, he outlined his theory in an article published in *Oncology*. "The silence was deafening," he recalls.

A year later, by a remarkable coincidence, Gold heard biochemist Paul Ray deliver a paper explaining that hydrazine sulfate could shut down the enzyme necessary for the production of glucose from lactic acid. Gold had chanced upon an eminently logical way of starving cancer. He immediately tested hydrazine sulfate on mice and found that in accord with his theory, the drug inhibited both gluconeogenesis *and* tumor growth.

Over the years, many dramatic remissions in patients on hydrazine sulfate therapy have been reported. In one case, a sixty-two-year-old woman with widely disseminated cancer of the cervix, in a very debilitated condition, was put on the drug. After one week, a secondary tumor the size of an orange had completely disappeared, much to the amazement of the woman's doctors, and neck nodes had become markedly smaller. After three weeks on the therapy, the patient had gained weight and was active and in good spirits. The woman was discharged from the hospital a short time later.[6]

In 1987, Erna Kamen, a sixty-three-year-old lung cancer patient, was administered hydrazine sulfate after her discharge from a Sarasota, Florida, hospital. "Basically, my mother was sent home to die," says Jeff Kamen, an Emmy-winning television reporter. "She'd lost a significant amount of weight by then, and she had no appetite and virtually no will to do anything."

A doctor had told Jeff's father, Ira Kamen, that hydrazine sulfate offered at least "a shot in the dark." So one Monday in August 1987 a home nurse gave Mrs. Kamen one hydrazine sulfate pill shortly before serving lunch. "On Tuesday morning," recalls Jeff, "there was a commotion in the house. My mother had risen from her bed like the phoenix rising from the ashes. She was demanding that the nurse bring her downstairs so that she could have breakfast with me. . . . When people you love get into this kind of facedown with death you're just incredibly grateful for each moment."[7]

As Jeff describes his mother's recovery, "her searing pain was gone, her appetite returned at a gallop." Within three weeks, her racking cough had vanished and she could walk unaided. "In the months before her death, she went on television with me to tell the nation about hydrazine sulfate. The National Cancer Institute stopped trashing hydrazine sulfate and began referring inquiries to the UCLA Medical School team whose work had validated the effectiveness of the drug long before Erna Kamen began taking it."[8] Jeff attributes his mother's death months later to her being "mistakenly taken off hydrazine sulfate and subjected to an unproven experimental substance."

With cancer patients, hydrazine sulfate is usually administered orally in 60-milligram capsules or tablets, approximately one to two hours before meals. It is given at first once a day for several days, then twice a day, then three or four times daily, depending on the patient's response and the physician's judgment. On such a regimen, many terminal and semiterminal patients have derived considerable benefit, although patients in the early stages of the disease derive the most benefit from the treatment.

Approximately half of the patients to whom the drug is properly administered in the early stages of the disease show an almost immediate weight gain and reversal of symptoms; in some instances, the tumor eventually disappears. The common types of cancer most frequently reported to benefit from hydrazine sulfate therapy are recto-colon cancer, ovarian cancer, prostatic cancer, lung (bronchogenic) cancer, Hodgkin's disease and other lymphomas, thyroid cancer, melanoma, and breast cancer. Some less common types of cancer also benefit.

"Whether hydrazine sulfate should be used in conjunction with other agents seems to be dependent on whether these agents are doing the patient any demonstrable good," according to Dr. Gold. "In the instances in which these agents have been doing good, hydrazine sulfate should be used in conjunction with them. However—and especially with those cases on toxic drugs—in instances in which the drugs have been doing no evident good, it is probably best to withdraw such drugs and use hydrazine sulfate alone." Many alternative therapists disagree. They see hydrazine sulfate as mainly an adjunctive treatment, albeit a potentially powerful one.

Critics have made much of the fact that hydrazine sulfate, a common industrial chemical, is found in such products as rocket fuel, insecticides, and rust-prevention agents. For medical purposes, however, the salt is refined, purified, and used in reagent-equivalent grades. Given to patients in minuscule amounts, it occasionally produces mild, transient side effects such as nausea, dizziness, itching of the skin, drowsiness, and euphoria, but such side effects are minimal, especially when compared with the devastating effects of standard chemotherapy.

A very small percentage of patients undergoing long-term, high-dosage hydrazine sulfate therapy experience pain or temporary numbness in their extremities, but this condition is quickly controlled by reducing the dosage and administering vitamin B_6. In no known cases has hydrazine sulfate depressed or destroyed white blood cells or bone marrow, as conventional chemotherapy often does. In general, toxicity has been exceedingly low or nil.

The most recent study of this drug, however, concluded that hydrazine sulfate appears not to be beneficial and may even have neurological side effects. This study involved a nationwide, twenty-month trial with 291 advanced non-small-cell lung cancer patients, all of whom received chemotherapy. In the double-blind phase, half were given hydrazine sulfate, while the other half received a placebo. Patients receiving hydrazine sulfate had a median survival of 7.62 months, while the

comparable figure for those on placebo was 7.5 months. Hydrazine sulfate had no effect on cancer cachexia, according to Michael Kosty, M.D., an oncologist with Scripps Clinic and Research Foundation in La Jolla, California, who was the study's principal investigator, nor were differences noted between the two groups in anorexia or weight gain. Furthermore, the placebo group rated their quality of life higher than did those patients taking hydrazine sulfate, and some hydrazine sulfate patients experienced loss of sensation and motor function. "Therefore, the best we can say about this drug is that it has no effect and may even be deleterious," Dr. Kosty was quoted as saying in a summer 1992 issue of *ASCO Highlights*, a publication of the American Society of Clinical Oncology.

Dr. Rowan Chlebowski, director of a UCLA research project on hydrazine sulfate, conservatively estimates that the drug could benefit about half a million cancer patients each year in the United States alone.[9] His team has conducted many clinical studies of hydrazine over two decades. Dr. Chlebowski says that the drug's indirect mode of action against tumors is problematic to more cautious investigators. "We found that hydrazine sulfate was an anticachexia agent that indirectly induced antitumor responses without much toxicity. Its action is not directed at cancer cells yet it may profoundly affect them."[10]

Dr. Chlebowski and his colleagues at the Harbor-UCLA Medical Center in Torrance, California, recently found evidence that hydrazine sulfate added to conventional chemotherapy improves the nutritional status and prolongs the life of patients with non-small-cell lung cancer, especially deadly forms of the disease. In the January 1990 issue of the prestigious *Journal of Clinical Oncology*, he reports that earlier-stage patients have a median survival time of at least 328 days, compared to 209 days for the placebo group. There is no curative therapy for this type of lung cancer, so the results, if confirmed, seem promising.

The wasting syndrome seen in cancer patients is also a prime risk factor for AIDS patients with Kaposi's sarcoma. There is evidence that hydrazine sulfate's capacity to stop cachexia may save many AIDS patients. Currently, Dr. Chlebowski is planning a study to test hydrazine sulfate as an anticachexia agent in patients who are infected with HIV and have lost weight.

Even though hydrazine sulfate is now undergoing extensive Phase III trials sponsored by the National Cancer Institute, resistance to this inexpensive, nontoxic chemotherapy in orthodox medical circles persists. Dr. Vincent DeVita, former director of NCI, told a

ashington Post reporter in 1988 that he thought hydrazine was a o-hum idea." Dr. Gold, until recently, has been frozen out of the ar on cancer." Two articles on cachexia published in July 1990 in e prestigious *Cancer Research* journal fail to reference any of Gold's th-breaking work, and one even denies there is any effective eatment for the wasting-away syndrome.

Dr. Gold, who does not treat patients, says that the cost of hydra- ne, at most, should be nominal—comparable to the daily cost of sulin and other supplies for diabetics. "Until a pharmaceutical com- ny sponsors the drug through the FDA, it will not be widely in use," predicts, adding, "However, with the new studies, drug companies ve suddenly begun to take notice of this most exemplary drug."

Resources

Syracuse Cancer Research Institute
Presidential Plaza
600 East Genesee Street
Syracuse, NY 13202
Phone: 315-472-6616

r further information on hydrazine sulfate and details on treatment.

eading Material

he Cancer Industry: Unravelling the Politics, by Ralph W. Moss (see ppendix A for description).

Part Two

IMMUNE THERAPIES

The immune system is your body's major line of defense in the battle against cancer and infection. Specialized cells in your immune system can recognize cancer cells as foreign and destroy them. The aim of immune therapies is to bolster those parts of the immune system that combat and eliminate cancer cells. Most other alternative therapies, though not strictly immunotherapies, also stimulate the body's natural defenses.

Several forms of orthodox immunotherapy are currently being explored in clinics and cancer centers. They are still used almost totally as adjuncts to chemotherapy, radiation, and surgery. While these orthodox immune therapies are said to hold great promise, they remain largely experimental. In contrast, the three alternative immune therapies discussed in Part Two of *Options* are used by many patients as full-fledged programs, though these treatments have been condemned, persecuted, or shunned by the medical establishment without an in-depth investigation into their possible merit. Most conventional physicians, trained to be aggressive in their approach to fighting disease, are cool toward the idea of strengthening the body's gentle self-healing powers and its natural resistance to cancer.

Cancer cells are believed to form every day in the healthy person, but a strong immune system can easily detect and destroy them before they have an opportunity to divide and proliferate. Unfortunately, for various reasons—poor nutrition, the massive pollution in our environment, stress, aging—the immune system sometimes fails to recognize the cancer cells as an enemy, and the cancer begins its slow, insidious growth over a number of years while you continue to be unaware of it.

Your immune system is normally on constant alert, scanning your body for "foreigners" such as bacteria, viruses, and abnormal cells. As soon as a foreign body is recognized, your whole system springs into action. Highly mobile *natural killer cells*, specialized to destroy foreign-

ers, are your body's first line of defense. If the cancer cells evade the natural killer cells, they proliferate and manufacture *antigens,* which are telltale substances detected by the *T-cells,* your immune system's second line of defense against tumor growth. Specialized T-cells (or *T-lymphocytes*) destroy cancerous and virus-infected cells. (The "T" in *T-cell* stands for "thymus-derived" because these white blood cells, created in the bone marrow, are carried to the thymus gland, which transforms them into T-cells.) Other white blood cells, *macrophages* (Greek for "big eaters"), ingest the cancer cells. A wide range of other cells and substances that make up the immune system help to orchestrate a coordinated attack against almost any invader.

Altogether, there are five major types of orthodox immunotherapy. The first is *BCG,* a tuberculin vaccine used in the treatment of cancer that stimulates macrophages to kill cancer cells. Consisting of a weakened strain of the tuberculosis bacillus, BCG (which stands for *bacillus Calmette-Guérin*) apparently works best when combined with chemotherapy; yet as a solo treatment, it has brought about some complete remissions and many cases of temporary or prolonged remission. Used by conventional as well as alternative doctors, BCG has been particularly successful in treating malignant melanoma. It appears to work well when injected directly into tumors visible on the skin, though it has also been used to treat lung cancer and other forms of the disease. One of the researchers who discovered BCG's anticancer potential was Dr. Lloyd Old, who later became director of the Sloan-Kettering Institute for Cancer Research.

Interferon is a family of proteins produced by the white blood cells in response to viral infection. It stimulates the production of macrophages and *lymphocytes* (white cells), blocks the growth of tumor cells, and transforms some lymphocytes into natural killer cells. Hyped as a wonder therapy and miracle cure when it was first synthesized in 1980, synthetic interferon turned out to be very expensive and have toxic side effects. It produces fever, chills, and muscle contractions so severe that they may require morphine.[1] Today, interferon is approved for use in the treatment of two rare forms of cancer, hairy-cell leukemia and juvenile laryngeal papillomatosis. It may have limited value in a number of other rare conditions. The FDA approved its use for AIDS patients in 1988, but it has largely been a failure in ARC-AIDS trials. Infected people who received it had flu-like symptoms, fatigue, swelling, headaches, and even hallucinations.

Interleukin-2, a protein produced by the T-cells, was also hyped by the cancer industry and the major news media as a cancer breakthrough. The results to date, however, have been disappointing. IL-2, as it is called, has reportedly been effective in some patients with melanoma

and renal cancer, but its drawbacks are major and became evident earl on. Charles Moertel, M.D., of the Mayo Clinic, charged that IL-2 is highl toxic, hugely expensive, and not particularly effective.[2] Its side effect include fever, chills, malaise, swelling of the spleen, anemia requirin multiple transfusions, severe bleeding, shock, and confusion. Treatmen with IL-2, according to Dr. Moertel, may require weeks of hospitalizatio in an intensive care unit "to survive the devastating toxic reactions." After a few patients died because of interleukin-2, the National Cance Institute, which had eagerly presented it to the public as a miracle drug withdrew such claims.[4]

Tumor necrosis factor (*TNF*), produced in the body in minute quantities seems to kill cancer cells by destroying their cell membranes, although wh this happens is not clear. Side effects occur regularly; most patients develo fever and chills as well as some nausea and vomiting.[5] Injected int cancerous mice, TNF causes their tumors to melt away. It is currently bein tested to determine its potential efficacy in treating human cancer patients Some observers believe that TNF, upon which the cancer establishmen has spent millions, is simply *tumor antibody,* one of the four blood fraction used by Lawrence Burton, pioneer of a nontoxic immune therapy used i the diagnosis and treatment of cancer (see Chapter 6).

Monoclonal antibodies are synthetic antibodies created through gene splicing, fusing a cancer patient's white blood cells with his or her cance cells. When these bizarre *hybridomas* are reintroduced into the patient' body, they manufacture specific antibodies said to attack only the cance cells. Attached to anticancer drugs or natural toxins, monoclonals serv as "guided missiles" by directing the antibodies they manufacture towar their malignant prey. Still in the investigative stage, monoclonals—lik interferon, interleukin-2, and TNF—promise to be tremendously exper sive, a boon to the pharmaceutical-medical monopoly if they are eve used in cancer treatment. They are frequently touted by the media as th next cancer breakthrough.

The American Cancer Society freely admits that it will take "man years to find the proper role of these [orthodox immunotherapy] agent in cancer treatment."[6] Observers say this means twenty years or mor Meanwhile, the ACS continues to use its enormous power and influenc to restrict or suppress safe, nontoxic cancer therapies that have pr duced remarkable clinical results in human beings, such as the immun therapies of Lawrence Burton, Ph.D. (Chapter 6) and Virginia Livingsto M.D. (Chapter 7), or the biologically based therapy of Stanislaw Burzyn ski, M.D. (Chapter 2).

Ironically, *Coley's mixed bacterial vaccine,* which has perhaps show

a greater cure rate than any other cancer treatment, is totally unavailable. Dr. William Coley (1862–1936), an eminent New York City surgeon and Sloan-Kettering researcher, in the 1890s developed a vaccine made of bacterial toxins that activated immune-resistance mechanisms in cancer patients and cured hundreds. His daughter, Helen Coley Nauts, D.Sc., has preserved and carried forward his important work. Yet, despite the successful use of bacterial vaccines amply reported in the medical literature since the turn of the century, today's big drug companies have no interest in what they view as merely an unprofitable item.

Staphage Lysate, a nonspecific bacterial vaccine made from *staphylococci,* is legally sold today as a specific therapy for acute and chronic staphylococcal infections. Unofficially, it has been widely used by pragmatic doctors who have had encouraging results in treating multiple sclerosis, cancer, herpes, allergies, arthritis, asthma, and many other conditions.[7] Relatively inexpensive and almost totally nontoxic, Staphage Lysate can be inhaled, injected, or taken orally. It is known to increase the production of T-lymphocytes and to induce the natural formation of interferon and *interleukin-1,* the predecessor of interleukin-2.

Immune therapies, whether orthodox or alternative, are generally used as a treatment of last resort after patients have received toxic chemotherapy or radiation. Many doctors believe that the prior use of immune-destroying, often carcinogenic conventional treatments lowers a patient's chances for recovery through immune therapy. Chemotherapy often accomplishes the destruction of the immune system, and radiation can cause severe, prolonged immune deficiency. At any one time, there are thousands of cancer patients in the United States undergoing aggressive chemotherapy who would benefit from any immune-enhancing measures whatsoever, even supportive nutrition or vitamin supplementation.

158 **Bairam A et al.** Theophylline versus caffeine: comparative effects in treatment of idiopathic apnea in the preterm infant. J Pediatr. 1987;110:636.

159 **Davis JM et al.** Use of caffeine in infants unresponsive to theophylline in apnea of prematurity. Pediatr Pulmonol. 1987;3:90.

160 **Eisenberg MG, Kang N.** Stability of citrated caffeine solutions for injectable and enteral use. Am J Hosp Pharm. 1984;41:2405.

161 **Eyal F et al.** Aminophylline versus doxapram in idiopathic apnea of prematurity: a double-blind controlled study. Pediatrics. 1985;75:709.

162 **Peliowski A, Finer NN.** A blinded, randomized, placebo-controlled trial to compare theophylline and doxapram for the treatment of apnea of prematurity. J Pediatr. 1990;116:648.

163 **Bairam A et al.** Doxapram for the initial treatment of idiopathic apnea of prematurity. Biol Neonat. 1992;61: 209.

164 **Barrington KJ et al.** Dose-response relationship of doxapram in the therapy for refractory idiopathic apnea of prematurity. Pediatrics. 1987;80:22.

165 **Tay-Uyboco J et al.** Clinical and physiological responses to prolonged nasogastric administration of doxapram for apnea of prematurity. Biol Neonate. 1991;59:190.

166 **Papile LA.** Central nervous system disturbances, part four: periventricular-intraventricular hemorrhage. In: Fanaroff AA, Martin RJ, eds. Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant. 5th ed. St. Louis: Mosby Year Book; 1992:719.

167 **Papile LA, Brann BS IV.** Intracranial hemorrhage: periventricular, intraventricular hemorrhage. In: Pomerance JJ. Richardson CJ, eds. Neonatology for the Clinician. Norwalk: Appleton & Lange; 1993:425.

168 **Volpe JJ.** Intraventricular hemorrhage and brain injury in the premature infant: neuropathology and pathogenesis. Clin Perinatol. 1989;16:361.

169 **Minarcik CJ Jr, Beachy P.** Neurologic disorders. In: Merenstein GB, Gardner SL, eds. Handbook of Neonatal Intensive Care. 3rd ed. St. Louis: Mosby Year Book; 1993:430.

170 **Volpe JJ.** Intraventricular hemorrhage and brain injury in the premature infant: diagnosis, prognosis, and prevention. Clin Perinatol. 1989;16:387.

171 **Lamp KC, Reynolds MS.** Indomethacin for prevention of neonatal intraventricular hemorrhage. DICP, Ann Pharmacother. 1991;25:1344.

172 **Ment LR et al.** Low-dose indomethacin and prevention of intraventricular hemorrhage: a multicenter randomized trial. Pediatrics. 1994;93:543.

173 **Volpe JJ.** Brain injury caused by intraventricular hemorrhage: is indomethacin the silver bullet for prevention? Pediatrics. 1994;93:673.

174 **Rust RS, Volpe JJ.** Neonatal seizures. In: Dodson WE, Pellock JM, eds. Pediatric Epilepsy: Diagnosis and Therapy. New York: Demos; 1993:107.

175 **Mizrahi EM.** Consensus and controversy in the clinical management of neonatal seizures. Clin Perinatol. 1989; 16:485.

176 **Painter MJ.** Therapy of neonatal seizures. Cleve Clin J Med. 1988;56 (Suppl.):S124.

177 **Morrison A.** Neonatal seizures. In: Pomerance JJ, Richardson CJ, eds. Neonatology for the Clinician. Norwalk: Appleton & Lange; 1993:411.

178 **Haymond MW.** Hypoglycemia in infants and children. Endocrinol Metab Clin North Am. 1989;18:221.

179 **Tsang RC.** Neonatal magnesium disturbances. Am J Dis Child. 1972;124: 282.

180 **Massingale TW, Buttross S.** Survey of treatment practices for neonatal seizures. J Perinatol. 1993;13:107.

181 **Painter MJ et al.** Phenobarbital and diphenylhydantoin levels in neonates with seizures. J Pediatr. 1978;92:315.

182 **Gilman JT et al.** Rapid sequential phenobarbital treatment of neonatal seizures. Pediatrics. 1989;83:674.

183 **Deshmukh A et al.** Lorazepam in the treatment of refractory neonatal seizures: a pilot study. Am J Dis Child. 1986;140:1042.

184 **McDermott CA et al.** Pharmacokinetics of lorazepam in critically ill neonates with seizures. J Pediatr. 1992; 120:479.

185 **Gal P et al.** Valproic acid efficacy, toxicity, and pharmacokinetics in neonates with intractable seizures. Neurology. 1988;38:467.

186 **Fischer JH et al.** Phenobarbital maintenance dose requirements in treating neonatal seizures. Neurology. 1981;31: 1042.

187 **Painter MJ et al.** Phenobarbital and phenytoin in neonatal seizures: metabolism and tissue distribution. Neurology. 1981;31:1107.

188 **Rosen TS.** Infants of addicted mothers. In: Fanaroff AA, Martin RJ, eds. Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant. 5th ed. St. Louis: Mosby Year Book; 1992:574.

189 **Finnegan LP, Weiner SM.** Drug withdrawal in the neonate. In: Merenstein GB, Gardner SL, eds. Handbook of Neonatal Intensive Care. 3rd ed. St. Louis: Mosby Year Book; 1993:40.

190 **Levy M, Spino M.** Neonatal withdrawal syndrome: associated drugs and pharmacological management. Pharmacotherapy. 1993;13:202.

191 **Doberczak TM et al.** Neonatal opiate abstinence syndrome in term and preterm infants. J Pediatr. 1991;118:933.

192 **Zelson C et al.** Neonatal narcotic addiction: comparative effects of maternal intake of heroin and methadone. N Engl J Med. 1973;289:1216.

193 **Greenglass EJ.** The adverse effects of cocaine on the developing human. In: Yaffe SJ, Aranda JV, eds. Pediatric Pharmacology: Therapeutic Principles in Practice. Philadelphia: WB Saunders; 1992:598.

194 **Neuspeil DR, Hamel BC.** Cocaine and infant behavior. J Dev Behav Pediatr. 1991;12:55.

195 **Kandall SR, Gartner LM.** Late presentation of drug withdrawal symptoms in newborns. Am J Dis Child. 1974;127:58.

196 **Finnegan LP et al.** Management of neonatal narcotic abstinence utilizing a phenobarbital loading dose method. Natl Inst Drug Abuse Res Monogr Ser. 1979;27:247.

197 **American Academy of Pediatrics, Committee on Drugs.** Neonatal drug withdrawal. Pediatrics. 1983;72:895.

198 **Wijburg FA et al.** Morphine as an anti-epileptic drug in neonatal abstinence syndrome. Acta Paediatr Scand. 1991;80:875.

199 **Hill RM, Desmond MM.** Management of the narcotic withdrawal syndrome in the neonate. Pediatr Clin North Am. 1963;10:67.

200 **Stark AR et al.** Muscle relaxation in mechanically ventilated infants. J Pediatr. 1979;94:439.

201 **Crone RK, Favorito J.** The effects of pancuronium bromide on infants with hyaline membrane disease. J Pediatr. 1980;97:991.

202 **Buck ML, Reed MD.** Use of non-depolarizing neuromuscular blocking agents in mechanically ventilated patients. Clin Pharm. 1991;10:32.

203 **Carlo WA et al.** Assisted ventilation and the complications of respiratory distress. In: Fanaroff AA, Martin RJ, eds. Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant. 5th ed. St. Louis: Mosby Year Book; 1992: 827.

204 **Taylor P.** Agents acting at the neuromuscular junction and autonomic ganglia. In: Gilman AG et al., eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 8th ed. New York: Pergamon Press; 1990:166.

205 **Bennett EJ et al.** Pancuronium and the neonate. Br J Anaesth. 1975;47:75.

206 **Greenough A et al.** Investigation of the effects of paralysis by pancuronium on heart rate variability, blood pressure and fluid balance. Acta Paediatr Scand. 1989;78:829.

207 **Cabal LA et al.** Cardiovascular and catecholamine changes after administration of pancuronium in distressed neonates. Pediatrics. 1985;75:284.

208 **Piotrowski A.** Comparison of atracurium and pancuronium in mechanically ventilated neonates. Intensive Care Med. 1993;19:401.

209 **American Academy of Pediatrics.** Committee on fetus and newborn, committee on drugs, section on anesthesiology, section on surgery. Neonatal anesthesia. Pediatrics. 1987;80:446.

210 **Anand KJS, Hickey PR.** Pain and its effects in the human neonate and fetus. N Engl J Med. 1987;317:1321.

211 **Shapiro C.** Pain in the neonate: assessment and intervention. Neonatal Netw. 1989;8:7.

212 **Goldberg RN et al.** Detection of seizure activity in the paralyzed neonate using continuous monitoring. Pediatrics. 1982;69:583.

213 **Zenk KE.** Practical pharmacology for the clinician caring for the newborn. In: Pomerance JJ, Richardson CJ, eds. Neonatology for the Clinician. Norwalk: Appleton & Lange; 1993:59.

214 **Roth B et al.** Analgesia and sedation in neonatal intensive care using fentanyl by continuous infusion. Dev Pharmacol Ther. 1991;17:121.

215 **Norton SJ.** After effects of morphine and fentanyl analgesia: a retrospective study. Neonatal Netw. 1988;7:25.

216 **Arnold JH et al.** Changes in the pharmacodynamic response to fentanyl in neonates during continuous infusion. J Pediatr. 1991;119:639.

217 **Katz R et al.** Prospective study on the occurrence of withdrawal in critically ill children who receive fentanyl by continuous infusion. Crit Care Med. 1994;22:763.

218 **Lane JC et al.** Movement disorder after withdrawal of fentanyl infusion. J Pediatr. 1991;119:649.

219 **Anand KJS, Arnold JH.** Opioid tolerance and dependence in infants and children. Crit Care Med. 1994;22:334.

220 **Watling SM, Dasta JF.** Prolonged paralysis in intensive care unit patients after the use of neuromuscular blocking agents: a review of the literature. Crit Care Med. 1994;22:884.

221 **Anyebuno MA, Rosenfeld CR.** Chloral hydrate toxicity in a term infant. Dev Pharmacol Ther. 1991;17:116.

222 **Mayers DJ et al.** Chloral hydrate disposition following single-dose administration to critically ill neonates and children. Dev Pharmacol Ther. 1991; 16:71.

223 **Mayers DJ et al.** Sedative/hypnotic effects of chloral hydrate in the neonate: trichloroethanol or parent drug? Dev Pharmacol Ther. 1992;19:141.

224 **Nahata MC, Hipple TF.** Pediatric Drug Formulations. 2nd ed. Cincinnati, OH: Harvey Whitney Books; 1992.

225 **Blumer JL, Reed MD.** Principles of neonatal pharmacology. In: Yaffe SV, Aranda JV, eds. Pediatric Pharmacology: Therapeutic Principles in Practice. 2nd ed. Philadelphia: WB Saunders; 1992:164, 168.

226 **Ernst JA et al.** Osmolality of substances used in the intensive care nursery. Pediatrics. 1983;72:347.

227 **White KC, Harkavy KL.** Hypertonic formula resulting from added oral medications. Am J Dis Child. 1982;136: 931.

228 **American Academy of Pediatrics, Committee on Drugs.** "Inactive" ingredients in pharmaceutical products. Pediatrics. 1985;76:635.

229 **Glasgow AM et al.** Hyperosmolality in small infants due to propylene glycol. Pediatrics. 1983;72:353.

230 **Balistreri WF et al.** Lessons from the E-Ferol tragedy. Pediatrics. 1986;78: 503.

231 **Kumar A et al.** The mystery ingredients: sweeteners, flavorings, dyes, and preservatives in analgesic/antipyretic, antihistamine/decongestant, cough and cold, antidiarrheal, and liquid theophylline preparations. Pediatrics. 1993; 91:927.

232 **Nahata MC.** Intravenous infusion conditions: implications for pharmacokinetic monitoring. Clin Pharmacokinet. 1993;24:221.

233 **Roberts RJ.** Issues and problems associated with drug delivery in pediatric patients. J Clin Pharmacol. 1994;34: 723.

234 **Nahata MC et al.** Effect of infusion methods on tobramycin serum concentrations in newborn infants. J Pediatr. 1984;104:136.

235 **Painter MJ et al.** Neonatal Seizures. Pediatr Clin North Am. 1986;33:95.

236 **Friedman WF.** Congenital heart disease in infancy and childhood. In: Braunwald E, ed. Heart Disease: A Textbook of Cardiovascular Medicine. 4th ed. Philadelphia: WB Saunders; 1992:893.

Hydrazine Sulfate in Cancer Patients With Weight Loss

A Placebo-Controlled Clinical Experience

ROWAN T. CHLEBOWSKI, MD, PHD,* LINDA BULCAVAGE, MN, RN,* MARY GROSVENOR, RD, MS,†
RAYNELLE TSUNOKAI, BS,* JEROME B. BLOCK, MD,* DAVID HEBER, MD, PHD,‡
MICHELLE SCROOC, RD,† JOAN S. CHLEBOWSKI, MD,§ JOCELYN CHI, MD,*
ENGIN OKTAY, MD,§ STEVE AKMAN, MD,* AND ISHRAT ALI, MD§

Hydrazine sulfate was evaluated using 24-hour dietary recalls and body weight determinations before and after 30 days of either placebo or hydrazine (60 mg, 3 times/d) oral administration in 101 heavily pretreated cancer patients with weight loss. After 1 month, 83% of hydrazine and only 53% of placebo patients completing repeat evaluation maintained or increased their weight ($P < 0.05$). In addition, appetite improvement was more frequent in the hydrazine group (63% *versus* 25%, $P < 0.05$). Although caloric intake was only slightly greater in hydrazine-treated patients, an increased caloric intake was more commonly associated with weight gain in patients receiving hydrazine compared with those receiving placebo (81% *versus* 53%, respectively). Hydrazine toxicity was mild, with 71% of patients reporting no toxic effects. Hydrazine sulfate circulatory levels were obtained from a subset of 14 patients who completed 30 days of treatment, with a single sample obtained in the morning at least 9 hours after the last dose. Mean maintenance hydrazine sulfate levels, determined using a spectrofluorometric assay, ranged from 0 to 89 ng/ml (mean 45 ± 16 ng/ml). These data, which demonstrate an association between 1 month of hydrazine sulfate administration and body weight maintenance in patients with cancer, suggest future clinical trials of hydrazine sulfate are indicated to definitively assess its long-term impact on important clinical outcome parameters in defined cancer populations.

Cancer 59:406–410, 1987.

WEIGHT LOSS commonly accompanies cancer development and is associated with an adverse prognosis.[1-3] Although intensive caloric support now can be provided such patients, clinical trials evaluating caloric provision alone have not reported improved outcome for chemotherapy-treated populations with advanced cancer.[4-6] As a result, consideration of potential mechanisms underlying the development of weight loss in the cancer population has led to development of alternative strategies for clinical intervention in these patients. Altered glucose metabolism is a common metabolic abnormality in cancer patients with weight loss,[7-13] and it has been suggested that the inappropriate activation of pathways of glucose metabolism leads to futile cycling and cachexia development in this population.[14] If this hypothesis is correct, amelioration of the abnormal carbohydrate metabolism could provide a therapeutic approach to the adverse outcome associated with cachexia development in the cancer-bearing host.

We previously demonstrated that hydrazine sulfate is metabolically active, improving the abnormal glucose tolerance and reducing the increased glucose production rates seen in cancer patients with weight loss.[13] We now report clinical observations on short-term hydrazine sulfate use in a cancer population with weight loss using a prospective placebo-controlled study design.

Materials and Methods

The criteria for inclusion in this trial were: a diagnosis of advanced cancer; weight loss greater than 10% from usual body weight; absence of severe hepatic or renal dysfunction (bilirubin greater than 3 mg/dl and/or creatinine greater than 2 mg/dl); and normal mental status. Patients with a known history of diabetes mellitus or those receiving corticosteroid therapy were ineligible. Patients with ascites or clinically significant edema were not entered to avoid confounding weight determinations. Patients were entered either prior to receiving systemic chemotherapy or when a new systemic therapy program was initiated

From the UCLA School of Medicine, Department of Medicine, *Division of Medical Oncology and †Clinical Research Center, Harbor-UCLA Medical Center, Torrance, and the ‡UCLA School of Medicine, Department of Medicine, Division of Clinical Nutrition, and the §Southern California Permanente Medical Group, Los Angeles, California.

Supported in part by Grant CA37320 from the National Cancer Institute, NIH; Grant RD-163 from the American Cancer Society; and Grant RR-00425 (General Clinical Research Center) from the NIH.

Address for reprints: Rowan T. Chlebowski, MD, PhD, Division of Medical Oncology, Harbor-UCLA Medical Center, 1000 West Carson Street, Torrance, CA 90509.

Accepted for publication September 9, 1986.

for disease progression. Measurable disease parameters were not required, and concurrent chemotherapy was permitted. Both initial and repeat assessment of all study parameters, however, were conducted at least 2 days before and 4 weeks after chemotherapy administration.

After informed consent was obtained, patients underwent an initial assessment of nutritional parameters, including caloric intake as described below. Patients subsequently were treated with capsules containing hydrazine sulfate (60 mg) or placebo which were prepared by Anabolic, Inc. (Irvine, California). Hydrazine sulfate was given under IND 17, 671 from the Food and Drug Administration (FDA) (obtained by Dr. Chlebowski). All institutional requirements for human subjects review were met. The treatment program consisted of an escalating schedule of capsules containing either hydrazine sulfate or placebo until the full dosage of 60 mg, 3 times/d given before meals, was reached beginning on the 8th day. This program was based on the extensive Russian experience.[15] Patients were contacted weekly to assess compliance and kept daily compliance diaries. The validity of daily compliance diaries was checked against intake based on returned prescription bottles. Following 30 days of either agent, the assessment of body weight, caloric intake, and other parameters was repeated.

During the initial and repeat evaluation, all patients received determination of body weight measured on the same printing scale; anthropometrics, including tricep skinfold thickness, mid-arm muscle circumference, and serum albumin; caloric intake using a 24-hour dietary recall history obtained by nutritionists and computer analyzed to give protein, carbohydrate, fat, and energy contents of the diet. Expected caloric intake was normalized for each patient by weight based on a calculated recommended daily allowance (RDA). Toxic effects of treatment and influence on appetite were determined by questionnaire.

In a subset of 14 patients, blood samples for hydrazine sulfate circulatory levels were obtained as a morning sample taken at least 9 hours from the last oral dose following 30 days of treatment. Hydrazine sulfate levels were measured using a defined[16,17] spectrofluorometric assay in which reaction of hydrazine sulfate with dimethylaminobenzaldehyde produces a colored derivative. Fluorescence was subsequently determined in an Aminco Bowman (Silver Spring, MD) spectrophotofluorometer with an excitation wavelength of 466 nm and emission wavelength of 546 nm.

All patients were given defined, uniform dietary counselling based on nutritional status at entry to insure comparability of dietary information available to patients on hydrazine or placebo treatment. The nutritional guidelines all patients were provided with were designed to duplicate a routine clinical dietary assessment that would be expected to be a component of a cancer patient's standard clinical management. Enteral tube feedings or parenteral nutritional support was not given any patient while on study.

TABLE 1. Pretreatment Characteristics of Cancer Patients Receiving Hydrazine Sulfate or Placebo

	Treatment received	
	Hydrazine	Placebo
Number entered	71	30
Age in years		
Median	56	59
Range	32–77	36–77
Sex (% Male)	61%	65%
Disease type		
Lung	46	15
Colon	13	4
Other breast	4	3
Esophagus	2	3
Nasopharyngeal	3	1
Hepatocellular	1	2
Ovarian	2	1
Prostate	0	1
Performance score		
(0 or 1)	14%	23%
(2 or 3)	86%	77%
Nutritional status		
% Weight loss (mean)	17%	14%
Caloric intake		
≥90% of RDA	39%	41%
<90% of RDA	61%	59%
Albumin gm/dl (Mean)	3.4	3.3
Concurrent chemotherapy	78%	74%

RDA: recommended daily allowance.

A total of 101 patients with advanced cancer underwent initial evaluation. Sixty-one consecutive patients (including all 30 patients given placebo and 31 given hydrazine) were randomly assigned treatment in a double-blind fashion with treatment assignment based on published random-number tables. An additional 40 patients received hydrazine sulfate and represented a consecutive series of patients seen in the Clinical Research Center meeting entry criteria for the trial. Statistically significant differences between hydrazine and placebo groups relative to pretreatment clinical factors were sought using chi square contingency table analyses and Student's *t* test. The statistical differences between hydrazine and placebo treatment were determined using the two-group *t* test.

Results

A total of 101 patients with a variety of advanced cancers underwent initial evaluation. Patients receiving hydrazine sulfate or placebo were comparable with respect to tumor type, age, sex, performance score, nutritional parameters and chemotherapy experience (Tables 1 and 2). The compromised nutritional status of the study pop-

TABLE 2. Concurrent Chemotherapy of Cancer Patients Receiving Hydrazine Sulfate or Placebo According to Disease Type

	Study arm	
Chemotherapy given	Hydrazine	Placebo
Lung cancer (n)	46	15
PACcO	15	4
PVB	12	7
ACcO	9	2
ACO	2	0
No chemotherapy	8	2
Colon cancer (n)	13	4
5-FU	2	1
5-FU + vitamin K	7	1
No chemotherapy	4	2
Other disease sites (n)*	12	11
No chemotherapy	4	3

P: cisplatin (Platinol); A: doxorubicin, (Adriamycin); C: cyclophosphamide; c: CCNU; O: vincristine (Oncovin); 5-FU: 5-fluorouracil; V: vinblastine; B: bleomycin; 5-FU + vit K: 5-fluorouracil plus vitamin K_3 (Synkavite).

* The patients with other disease sites received a variety of regimens which included cisplatin in 62% and 50% of instances for the hydrazine and placebo group, respectively.

ulation is demonstrated by the 16% average weight loss experienced by the overall population. Of this advanced disease population with weight loss, 58 patients were able to complete repeat evaluations after 30 days of treatment (41 were given hydrazine; 17, placebo). Early disease progression and/or death accounted for almost all cases not having repeat study. Only two patients refused repeat evaluation.

The influence of 30 days of hydrazine sulfate or placebo therapy on study parameters for all entered patients who underwent repeat evaluation is outlined in Table 3. Weight was maintained or increased in a higher proportion of patients receiving hydrazine sulfate compared to placebo therapy (83% *versus* 53%, respectively; $P < 0.05$). The use of weight loss as a study parameter was not compromised by the development of ascites or significant edema, as this did not occur in any patient over the 30 day period of observation. Anthropometrics were unchanged over the 30-day study period. Caloric intake was only slightly higher in the hydrazine treated population. When all patients experiencing an increase in caloric intake were considered, however, weight gain was seen in a significantly higher proportion of patients receiving hydrazine sulfate while increasing caloric intake compared with those who increased caloric intake while receiving placebo. The results using hydrazine sulfate were closely comparable in the 31 patients entered as part of the randomized trial when compared with the 40 patients added as a consecutive series. The results for the patients receiving hydrazine or placebo who were entered as part of the randomized trial were: weight maintained or increased, 71% *versus* 53%; improvement in appetite, 63% *versus* 25%; caloric intake increased, 69% *versus* 37%; and increased caloric intake associated with weight gain, 77% *versus* 53% for the hydrazine *versus* placebo patients respectively. In addition, results in groups receiving or not receiving concurrent chemotherapy reflected those obtained in the entire group.

TABLE 3. Influence of 30 Days of Hydrazine Sulfate or Placebo on Nutritional Status of Cancer Patients With Weight Loss

	Hydrazine n = 41*	Placebo n = 17
Weight maintained or increased (>2.5 kg)	83%†	53%
Improvement in appetite	63%†	25%
Caloric intake increased (>10% over baseline)	51%	37%
Increased caloric intake associated with weight gain (>2.5 kg)	81%†	53%

* Number completing initial and repeat study.
† $P < 0.05$ hydrazine compared to placebo group.

Thirty-five patients with cancer other than small cell lung cancer (the predominant tumor type studied) completed serial evaluation, with 26 receiving hydrazine sulfate and nine receiving a placebo. In the lung cancer patients, weight maintenance or increase was achieved in 83% of those receiving hydrazine sulfate compared with 33% of those receiving the placebo.

The short term hydrazine sulfate regimen used in this trial was well tolerated by study participants. Compliance forms were returned by 90% of patients who completed repeat evaluations, and indicated that 95% of the scheduled dose was taken by the study population completing 30 days of therapy. The mean maintenance plasma hydrazine sulfate levels obtained from a subset of 14 patients ranged from 0 to 89 ng/ml with a mean value of 45 ± 16 ng/ml. Clinical toxicity of patients receiving hydrazine sulfate was limited largely to mild to moderate nausea and lightheadedness with 71% of patients reporting no toxic effects from hydrazine use (Table 4). Treatment was discontinued for toxic effects in 10% of patients receiving hydrazine; while 6% of patients receiving placebo had treatment stopped for "toxic effects." Significantly, parasthesias or hypoglycemic symptoms were not reported by any patient receiving hydrazine in this trial.

Discussion

Short-term administration of hydrazine sulfate was better than a placebo in maintaining body weight and improving appetite in patients with advanced cancer in the current clinical experience. The weight effect apparently resulted from an increase in the effectiveness of the ingested calories, since a higher proportion of patients

who increased their caloric intake on hydrazine were able to maintain or improve their body weight. The association that we have reported[18] between weight maintenance and improved glucose metabolism in hydrazine-treated cancer patients suggests that interruption of abnormal metabolic pathway function may underlie the improved nutritional status seen with hydrazine sulfate in the current trial. If this hypothesis can be confirmed, hydrazine sulfate could represent one of a new class of metabolic/hormonal agents[19–21] directed at influencing the abnormal metabolism seen frequently in patients with cancer.

No prior clinical experience with hydrazine sulfate in cancer patients has prospectively evaluated caloric intake or included a placebo control population. Single-arm studies involving 348 Russian and 84 American patients with cancer have emphasized subjective parameters.[15,22] In the American experience, Gold[22] reported that 70% of the treatment group demonstrated subjective improvement, including increased appetite with either weight gain or cessation of weight loss, increased strength and improved performance status, or decreased pain, as measured by need for analgesics. In the Russian experience, Gershonovich[15,23] reported that 50% of patients receiving hydrazine sulfate as their sole therapeutic intervention achieved moderate or marked improvement in cachexia with associated favorable symptomatic effects on appetite and pain. Not all clinical studies of hydrazine sulfate have shown benefit. In three small trials of hydrazine sulfate (all entering less than 30 patients) where reduction in tumor size was used as a major therapeutic endpoint, little benefit was reported.[24–26] The clinical effects of hydrazine sulfate on body weight observed in the current study in conjunction with the metabolic effects of hydrazine that we reported in 1984[12] now provides a strong rationale for further studies designed to assess the impact of hydrazine sulfate on clinical outcome in defined cancer populations.

Surprisingly, thirty-seven percent of weight-losing cancer patients given placebo in this trial increased their caloric intake by more than 10%, and 53% of the placebo group maintained or increased their body weight over the 1-month observation period. This result in the placebo population may have been related to the nutritional counseling that was given in identical fashion to patients on both treatment arms in this study. Placebo controls clearly are important in trials designed to alter and assess nutritional parameters in cancer populations.

The study protocol employed in our trial was not designed to assess the influence of hydrazine sulfate on tumor growth characteristics. The short 30-day period of treatment and entry criteria preclude assessment of hydrazine sulfate influence on this parameter. Almost all of our patients with advanced solid tumors refractory to initial therapy, however, demonstrated no change in tumor dimensions during the 1-month period of observation.

TABLE 4. Patient Tolerance of Hydrazine Sulfate or Placebo Treatment

	% of Patients Treated	
	Hydrazine	Placebo
No toxic effects	71%	84%
Nausea and vomiting		
Mild	12%	12%
Moderate	5%	0%
Light-headedness	17%	6%
Treatment discontinued for toxic effects	10%	6%

The relative lack of toxicity of short-term hydrazine sulfate administration in a 60 mg 3 times/d schedule to a large cancer population receiving other concurrent chemotherapy treatment was noteworthy. In the previous limited clinical experience,[15,22,23] only one report has emphasized significant toxicity; Ochoa and coworkers[24] reported a 50% incidence of polyneuritis associated with hydrazine sulfate use in a 29-patient experience. In three trials[15,22,25] and the present report, polyneuritis was seen in less than 1% of the more than 500-patient cumulative experience. The lack of toxicity in the current experience can be documented further by the good compliance reported by the patients in their diaries. The latter result is interesting considering the somewhat wide range of hydrazine sulfate maintenance circulatory levels observed in the pharmacokinetic component of this trial. However, these results are consistent with developing pharmacokinetic information regarding the half-time of oral hydrazine sulfate administration.[17] These data suggest that future clinical trials involving hydrazine sulfate should include determination of chronic circulatory levels to assess hydrazine sulfate bioavailability and permit correlation with metabolic, nutritional and clinical endpoints.

Conclusion

This experience with hydrazine sulfate in an advanced cancer population points to a potential role for this agent in maintaining weight in patients with cancer cachexia. Whether maintenance of body weight under these conditions will be associated with improvement in important clinical outcome variables and overall survival will require future prospective, long-term, placebo-controlled evaluation in cancer populations with less advanced disease given defined systemic therapy. Such studies in the non-small cell lung cancer population are currently in progress.

REFERENCES

1. DeWys WD, Begg C, Lavin PT *et al.* Prognostic effects of weight loss prior to chemotherapy in cancer patients. *Am J Med* 1980; 69:491–497.

2. Costa G, Lane WW, Vincent RG *et al.* Weight loss and cachexia in lung cancer. *Nutr Cancer* 1981; 2:98–103.

3. Chlebowski RT, Heber D, Block JB. Lung cancer cachexia. In Greco FA, ed. Lung Cancer II. The Hague: Martinus Nijhoff Publishers, 1983; 125–142.

4. Clamon G, Feld R, Evans WE, *et al.* Effect of hyperalimentation on the survival and response to treatment of patients with small cell lung cancer: a randomized trial. *Cancer Treat Rep* 1985; 69:167–177.

5. Nixon DW. Hyperalimentation in the undernourished cancer patient. *Cancer Res* 1982; (Suppl) 42:727s–728s.

6. Chlebowski RT. Critical evaluation of the role of nutritional support with chemotherapy. *Cancer* 1985; 55:268–272.

7. Rohdenberg GL, Bernhard A, Drehbiel O. Sugar tolerance in cancer. *JAMA* 1919; 72:1528–1529.

8. Holroyde CP, Gabuzda TG, Putnam RC *et al.* Altered glucose metabolism in metastatic carcinoma. *Cancer Res* 1975; 35:3710–3714.

9. Waterhouse C, Jeanpretre N, Keilson J. Gluconeogenesis from alanine in patients with progressive malignant disease. *Cancer Res* 1979; 39:1968–1972.

10. Lundholm K, Edstrom S, Karlberg I et al. Glucose turnover, gluconeogenesis from glycerol, and estimation of net glucose cycling in cancer patients. *Cancer* 1982; 50:1142–1150.

11. Chlebowski RT, Heber D, Block JB. Serial assessment of glucose metabolism in patients with cancer cachexia. *Clin Res* 1982; 30:69A.

12. Chlebowski RT, Heber D, Richardson B, Block JB. Influence of hydrazine sulfate on abnormal carbohydrate metabolism in cancer patients with weight loss. *Cancer Res* 1984; 44:857–861.

13. Chlebowski RT, Heber D. Metabolic abnormalities in cancer patients: Carbohydrate metabolism. In: Meguid M, Rudrick S, eds. *Surg Clin North Am* 1986; 66:957–968.

14. Gold J. Proposed treatment of cancer by inhibition of gluconeogenesis. *Oncology* 1968; 22:185–207.

15. Gershanovich ML. Clinical effects of hydrazine sulfate in patients with advanced malignant disease. In Filov VA, Evin BA, Gershanovich ML, eds. Medical Therapy of Tumors. Leningrad: USSR Ministry of Health, 1983; 91–183.

16. Vickers S, Stuart EK. Simple, sensitive spectrophotofluorometric method for hydrazine in plasma. *Anal Chem* 1974; 46:138–140.

17. Chlebowski RT, Dietrich M, Tsunokai R *et al.* Hydrazine sulfate clinical pharmacokinetics. *Proc Am Assoc Can Res* 1985; 26:254.

18. Chlebowski RT, Heber D, Richardson B *et al.* Association between improved carbohydrate metabolism and weight maintenance in hydrazine sulfate treated patients with cancer cachexia. *Proc Am Soc Clin Oncol* 1983; 2:C372.

19. Schein PS, Kisner D, Haller D *et al.* Cachexia of malignancy: Potential role of insulin in nutritional management. *Cancer* 1979; 43: 2070–2076.

20. Burt ME, Lowry SF, Gorschboth C *et al.* Metabolic alterations in a noncachetic animal tumor system. *Cancer Res* 1982; 42:774–781.

21. Lelli G, Angelelli B, Giambiasi ME *et al.* The anabolic effect of high dose medroxyprogesterone acetate in oncology. *Pharmacol Res Commun* 1983; 15:561–568.

22. Gold J. Use of hydrazine sulfate in terminal and preterminal cancer patients: results of investigational new drug (IND) study in 84 evaluable patients. *Oncology* 1975; 32:1–10.

23. Gershanovich ML, Danova LA, Ivin BA et al. Results of clinical study of antitumor action of hydrazine sulfate. *Nutr Cancer* 1981; 3:4–12.

24. Ochoa M, Wittes R, Krakoff I. Trial of hydrazine sulfate (NSC-150014) in patients with cancer. *Cancer Chemother Rep* 1975; 59:1151–1153.

25. Spemulli E, Wampler GL, Regelson W. Clinical study of hydrazine sulfate in advanced cancer patients. *Cancer Chemother Pharmacol* 1979; 3:121–124.

26. Lerner HJ, Regelson W. Clinical trial of hydrazine sulfate in solid tumors. *Cancer Treat Rep* 1976; 60:959–960.

Oncology 32: 1–10 (1975)

Use of Hydrazine Sulfate in Terminal and Preterminal Cancer Patients: Results of Investigational New Drug (IND) Study in 84 Evaluable Patients

Joseph Gold

Syracuse Cancer Research Institue. Syracuse, N.Y.

Key Words. Hydrazine sulfate therapy in advanced cancer patients · Treatment of advanced human cancer with anti-gluconeogenic drugs · Interruption of cancer cachexia as a means of cancer chemotherapy · Interruption of gluconeogenesis as a means of cancer chemotherapy

Abstract. In a series of 84 various evaluable disseminated cancer patients treated with hydrazine sulfate as a result of a pharmaceutical-sponsored investigational new drug (IND) study, it was found that 59/84 or 70 % of the cases improved subjectively and 14/84 or 17 % improved objectively. Subjective responses included increased appetite with either weight gain or cessation of weight loss, increase in strength and improved performance status and decrease in pain. Objective responses included measurable tumor regression, disappearance of or decrease in neoplastic-associated disorders and long-term (over 1 year) 'stabilized condition'. Of the overall 59 subjective improvements 25 (42 %) had no concurrent or prior (within 3 months) anticancer therapy of any type. Of the 14 objective improvements 7 (50 %) had no concurrent or prior anticancer therapy. Of the remaining cases in which there was either concurrent or prior anticancer therapy, improvements occurred only *after* the addition of hydrazine sulfate to the treatment regimen. Duration of improvement was variable, from temporary to long-term and continuing. Side effects were mild, comprising for the most part low incidences of extremity paresthesias, nausea, pruritis and drowsiness; there was no indication of bone marrow depression.

Hydrazine sulfate has been used as an investigational new drug (IND) for over 1 year in the treatment of advanced cancer. Its proposed mechanism of action is as a gluconeogenic blocking agent at the phosphoenolpyruvate carboxykinase (PEP CK) reaction, attenuating host energy loss as a result of increased gluconeogenesis in cancer and therefore interrupting the *systemic* cycle of *tumor-energy gain–host-energy loss* (tumor growth–host cachexia) (1, 2). Early reports indicated that hydrazine sulfate, administered orally to advanced cancer patients, resulted in marked subjective and objective improvements (3), subjective improvements including increase in appetite, cessation of weight loss and/or

weight gain, improved performance status, and decrease in pain; objective improvements included measurable reduction in tumor size and reduction in or disappearance of neoplastic-associated disorders (effusions, jaundice, etc.). Duration of improvements was reported as variable and side effects, minimal. In further reports (4), in which hydrazine sulfate was used in conjunction with conventional chemotherapy in patients with disseminated neoplasia, it was unclear as to which type of therapy resulted in the reported subjective and objective improvements. The present report, undertaken as a pharmaceutical-sponsored IND study and representing a series of 84 evaluable cases of various terminal and preterminal cancer patients, indicates a high degree of anticancer activity in patients treated with hydrazine sulfate alone.

Procedures and Protocols

Physician selection. This study was the result of separate inputs of many clinicians – oncologists as well as others – whose participation was under pharmaceutical IND sponsorship. As such, this study is designated as 'uncontrolled'.

Patient selection. Patients with any type of disseminated neoplasia, who no longer responded to chemotherapy and/or radiation, were considered eligible for hydrazine sulfate therapy. A minimum prognosis of 2 months was recommended.

Drug and protocol. The drug consisted of 100 % purity hydrazine sulfate mixed with an inert starch in capsular form (pharmaceutical IND preparation) for oral administration. Protocol of drug administration was as follows: 60 mg q.d. × 4; 60 mg b.i.d. × 4; then 60 mg t.i.d. as maintenance. In patients weighing less than 50 kg, dosages were halved (i.e., 30 mg q.d. × 4; 30 mg b.i.d. × 4; then 30 mg t.i.d.). In the event that a b.i.d. schedule produced satisfactory results, this dosage schedule was maintained at the clinician's discretion. In no event was a single dosage ever to exceed 60 mg.

Concurrent anticancer medication. The continuing use of concurrent anticancer medication was acceptable if it was no longer producing a demonstrable anticancer effect by itself.

Data presentation. A 4-sheet data page ('Patient Report Form') was required to be completed by the clinician during the course of treatment of each patient. These data sheets included the following information: detailed history, site of tumor and metastases, prior treatments (defined in this study as any type of anticancer therapy given within 3 months of the initiation of hydrazine sulfate therapy; prior treatment data included dates of therapy, types and quantitation), concurrent medications, performance status evaluation, objective tumor size and site evaluations, subjective observation ratings and check list, laboratory data, clinician's statement of patient evaluation prior to hydrazine sulfate therapy, clinician's statement of evaluation of results of hydrazine sulfate therapy, clinician's evaluation of side effects of hydrazine sulfate therapy, and clinician's signature.

Criteria for designation as 'improvement'. Designation of subjective improvements was made on the basis of improvements indicated in the subjective observations rating check list and/or affirmation of improvement in the clinician's statement under 'clinician evaluation' section. In general a subjective improvement was based on a quantitatively measurable or estimable parameter such as strength (number of hours ambulatory, quality of ambulation, etc.), appetite (food intake), weight (scale measurement) and pain (quantitative need for analgesics). Objective improvements were designated on the basis of measurable reduction in

tumor size, long-term (1 year or more) 'stabilized condition' in a previously rapidly growing neoplasm, and disappearance of or reduction in neoplastic-associated disorders. Each case in this category was to be supported by related laboratory measurements, where possible.

Criteria for designation as 'nonevaluable'. Cases were deleted from evaluation for any of the following reasons: (a) inadequate prognosis: patient survival of less than 3 weeks; (b) inadequate drug trial: drug trial of less than 3 weeks; (c) insufficient data submitted on Patient Report Form: no evaluation possible, and (d) concurrent treatment with newly initiated cytotoxic chemotherapy: patient response nonevaluable.

Results

Of a total number of 158 cases submitted in the study, 84 were evaluable and 74 nonevaluable. Of the evaluable cases 14 (17 %) were categorized as 'objective (and subjective) improvement', 45 (54 %) as 'subjective improvement only', and 25 (30 %) as 'no improvement'. The indicated overall improvement

Table I. **Categorization of evaluable cases in Investigational New Drug study of hydrazine sulfate**

Site and/or type of primary tumor	Objective and subjective improvements	Subjective improvement only	No improvement	Total cases
Brain (astro, glio)	2	0	0	2
Breast (all)	2	6	2	10
Colorectal-gastric	2	12	8	22
Gallbladder	1	0	0	1
Hodgkins, stage IV	0	0	2	2
Liver (primary)	0	0	1	1
Lung (all)	2	11	2	15
Melanoma	0	1	2	3
Neurosarcoma (neck)	0	1	0	1
Ovary (all)	1	3	1	5
Pancreas	1	4	3	8
Primary unknown	0	2	0	2
Prostate	0	1	2	3
Squamous cell (neck)	0	1	0	1
Testis	0	1	0	1
Tonsil (palatine)	1	0	0	1
Urinary bladder, ureter	0	1	2	3
Uterus (cervix)	1	1	0	2
Uterus (endometrial)	1	0	0	1
Total	14	45	25	84

Table II. Nonevaluable cases: reasons for exclusion from evaluation

Inadequate prognosis survival time, weeks			Inadequate drug trial, weeks on drug			Insufficient data	New concurrent cytotoxic chemotherapy	Total cases
0–1	1–2	2–3	0–1	1–2	2–3			
11	11	9	8	6	11			
31			25			15	3	74

rate was 59/84 cases, or 70 %. Of the nonevaluable cases, 31 (42 %) were included under 'inadequate prognosis', 25 (34 %) under 'inadequate drug trial', 15 (20 %) under 'insufficient data', and 3 (4 %) under 'newly initiated cytotoxic chemotherapy'. Categorization of evaluable and nonevaluable cases is given in tables I and II, respectively.

'Improvements'

Improvements were noted in tumors from almost all of the 19 reported sites of origin. No particular site of origin or tumor type was 'most susceptible' to hydrazine sulfate therapy, although the largest number of cases came from colorectal and lung carcinoma, which reflects the general incidence of these diseases in the population. The duration of improvement was variable, being reported from very temporary (1 week) to in excess of 1 year and continuing. It was possible to obtain follow-up reports in only less than half of the improved cases.

Objective responses. Of the 14 reported objective responses, 7 (50 %) showed measurable tumor regression; 2 of these were accompanied by a disappearance of or reduction in neoplastic-associated disorders (effusions, jaundice, etc.). An additional 2 (14 %) of the 14 cases were classified as long-term 'stabilized condition', both of which represented preterminal lung cancers whose disease had been rapidly progressive prior to hydrazine sulfate therapy. They are currently both alive and well 17 and 18 months after initiation of hydrazine sulfate therapy, respectively; neither are on any kind of concurrent anticancer therapy. The remainder of the 5 (36 %) cases were classified as objective responses on the basis of amelioration of neoplastic-associated disorders, accompanied by marked subjective improvements. (In this regard all 14 cases showed subjective improvements.) All objective responses were also accompanied by tumor-related laboratory improvements, where measured.

Subjective responses. A total of 45 cases displayed subjective improvements only; this number, added to the foregoing 14 cases, gave a combined total of 59 subjectively improved cases. 48 (81 %) of these showed an increase in appetite

Table III. Response analysis in improved cases

	No concurrent or prior anticancer therapy	Concurrent anticancer (incl. cytotoxic) therapy	Concurrent steroid therapy only	Concurrent steroid and prior cytotoxic therapy	Concurrent steroid and prior radiation therapy	Prior cytotoxic therapy	Prior steroid therapy	Prior radiation therapy	Total cases
Objective responses	7 (50 %)	3 (21 %)	1 (7 %)	–	1 (7 %)	–	1 (7 %)	1 (7 %)	14
Subjective responses	18 (40 %)	17 (38 %)	5 (11 %)	1 (2 %)	–	3 (7 %)	–	1 (2 %)	45

with either weight gain or a cessation of weight loss. 48 (81 %) showed an improvement in performance status as measured by an increase in strength, [illegible]bulation or both. And 21 (36 %) showed a decrease in pain as measured by a [illegible]inuted need for analgesics.

Ongoing concurrent (or prior) anticancer therapy. Various of the improved cases were treated with either steroids and/or cytotoxic chemotherapy and/or radiation, prior to initiation of hydrazine sulfate therapy, as indicated in table III. In all these cases the noted improvements occurred *after* the addition of hydrazine sulfate to the therapy. In regard to the objective responses 7 (50 %) of the 14 cases were treated with hydrazine sulfate alone, without concurrent or prior anticancer therapy of any type, while 7 (50 %) of the cases did receive concurrent or prior anticancer therapy. In the subjective-only responses, 18/45 or 40 % of the cases were treated only with hydrazine sulfate, without concurrent or prior anticancer therapy, while 27 of the cases (60 %) did receive concurrent or prior anticancer therapy.

'No Improvements'

Of the 25 'no improvement' cases 2 (8 %) expired within 3–4 weeks after initiation of hydrazine sulfate therapy; 2 (8 %) had very little information in their Patient Report Form so that actual categorization became difficult; 9 (36 %) had a drug trial of only 3–4 weeks, and 14 (56 %) had concurrent anticancer therapy which consisted of cytotoxic drugs, radiation, steroids or combinations thereof. *In only 5 cases* were these foregoing considerations not a factor, i.e., the patient had an adequate prognosis and drug trial, had no concurrent or prior anticancer therapy, and had sufficient information submitted on his Patient Report Form to support a categorization of 'no improvement'.

Nonevaluable Cases

The general breakdown of categories of the 74 nonevaluable cases is given above and in table II. Of a total of 31 of these cases excluded from evaluation because of inadequate prognosis (survival time), 11 died within 1 week of initiation of hydrazine sulfate therapy, 22 died within 2 weeks, and the full 31 died within 3 weeks. Of a total of 25 additional cases excluded from evaluation for reasons of inadequate drug trial, 8 were on drug for only 1 week or less, 14 were on drug for 2 weeks or less, and the full 25 were on drug for 3 weeks or less. Thus, of the 56 cases excluded from consideration for the foregoing two reasons, 19 had a survival time or drug trial of 1 week or less, 36 had a survival time or drug trial of 2 weeks or less, and the full number – 56 – had a survival time or drug trial of 3 weeks or less.

Side Effects

Side effects were determined on the basis of evaluable cases only and were in general mild. They comprised: *extremity paresthesias* (5 %); this condition was diminished or eliminated by a reduction of dosage and/or administration of pyridoxine hydrochloride (vitamin B_6) in excess of 25 mg daily; *nausea* (4 %), in most cases transient; nontransient nausea was eliminated by a reduction of dosage or withdrawal of medication for a period of several days, then reinstitution of treatment at lower dosage levels; *dry skin* or *transient pruritis* (3 %); *'dizziness'* (1 %); *'drowsiness'* (1 %); *possible thrombophlebitis* (1 %) (it was not known whether this condition was drug-related). The total evaluable cases showing side effects numbered 13/84 or an overall 15 %. There were no deaths attributable to hydrazine sulfate therapy, either in the evaluable or in the nonevaluable cases.

Discussion

It is important that a detailed analysis of a study of this nature include not only the obviously improved cases as a result of hydrazine sulfate administration, but also the nonimproved and nonevaluable cases. Such factors as poor patient and clinician selection as well as inadequate protocol planning, must be assessed as to their quantitative contribution to the latter two categories.

Nonimproved and Nonevaluable Cases

Lack of proper patient selection, via inadequate patient prognosis and inadequate drug trial, contributed heavily to the large number of nonevaluable and nonimproved cases. Minimum protocol-recommended prognosis was 2 months, yet as many as 31/74 or 42 % of the nonevaluable cases were so designated because of a survival time of 3 weeks or less, while in the nonimproved category

2/25 or 8 % of the cases had a survival time of only 3–4 weeks. In addition, as many as 25/74 or 34 % of the nonevaluable cases were so designated because of an inadequate drug trial (3 weeks or less), while 9/25 or 36 % of the nonimproved cases had a drug trial of only 3–4 weeks. Thus, in the nonevaluable category the number of combined inadequate prognosis and inadequate drug trial cases totaled 56/74 or 76 %, while in the nonimproved category the number of combined cases of 'borderline-acceptable' survival time and drug trial (3–4 weeks) totaled 11/25 or 44 %. Such large percentages, representing inadequate prognosis and inadequate drug trial, must be attributed chiefly to improper patient selection and not to the occasional misevaluations which arise in any study.

Lack of proper clinician selection was also an apparent factor in this study, manifest chiefly in those cases in which too little information was submitted. In the nonevaluable category as many as 15/74 or 20 % of the cases were so designated because of lack of sufficient information upon which to make an evaluation. Even in the nonimproved category 2/25 or 8 % of the cases had only a minimum of information submitted. Such numbers surely reflect a lack of interest or capability on the part of the clinician. (Indeed, inadequate patient selection itself may be a function of this type of clinician inadequacy.)

Poor protocol planning, manifest by the acceptability of concurrent anticancer therapy, also had a major input in these two categories. In the nonevaluable group 3/74 or 4 % of the cases were so designated because of newly initiated concurrent cytotoxic chemotherapy, rendering impossible any attributive evaluation of patient response. In the nonimproved group as many as 14/25 or 56 % of the cases had ongoing concurrent anticancer therapy which was no longer producing demonstrable clinical benefit, but which could, by virtue of its immunosuppressive and hematosuppressive effects, adversely affect or mask the results of any new drug concurrently administered. Clearly, the protocol was weakened by inclusion of any type of concurrent anticancer therapy whatsoever.

Thus, in retrospect many of the cases which fell into the nonevaluable and nonimproved categories should properly never have entered this study. This circumstance could have been obviated by better patient and clinician selection as well as by a 'tighter' protocol. It is hoped that a careful categorization in this study has dealt adequately with these factors.

Improved Cases

Despite the above-described considerations, a large number of clearly improved cases emerged in this study. This improvement, moreover, was the result of administration of hydrazine sulfate alone in a large percentage of the cases and was not influenced by any other mode of concurrent or prior anticancer therapy. Table III indicates that 50 % of the objectively improved cases (7/14) were on hydrazine sulfate alone, with no prior or concurrent anticancer therapy;

and 40 % (18/45) of the subjective-only responses were also the result of hydrazine sulfate therapy alone. This constitutes strong *prima faciae* evidence indicating hydrazine sulfate to be a clinically active anticancer agent in itself. It is important to remember that even in those cases which received concurrent or prior anticancer therapy, the noted improvements occurred only *after* the addition of hydrazine sulfate to the treatment regimen. Thus, whether as a sole agent or in combination with other agents, administration of hydrazine sulfate to advanced cancer patients is linked to marked anticancer responses.

Moreover, hydrazine sulfate is apparently not a 'tumor-specific' agent, as can be seen from table I. Virtually all types of cancer – especially those which ultimately promote a degree of host cachexia – are apparently susceptible to its actions. Reports, in addition to those of this study, which have reached this laboratory, indicate that the spectrum of disease beneficially affected by hydrazine sulfate extends to cancers arising from all organ systems and/or tissues in the body. The most dramatic responses reported to date have been those with primary lung neoplasms, although this observation may prove to be premature as more and earlier cases are reported.

The duration of improvement has been unpredictable, but has generally been longer in those cases responding objectively (as well as subjectively). Some of the responses have been of very short duration. But others have been quite lengthy. To date three cases in this study – two primary lung and one ovarian – are alive 17, 18 and 21 months after institution of hydrazine sulfate therapy alone, respectively; all three were previously considered terminal or preterminal. Preliminary indications suggest that the improvements brought about hy hydrazine sulfate therapy – whether objective or subjective – have been accompanied by extension in survival time and that the quality of this survival time was high: patients who had obtained objective response and/or increased appetite, strength and decreased pain as a result of hydrazine sulfate therapy, were reported to have been restored to a more positive orientation toward living.

The duration of improvement may also be related to the degree of advancement of the disease. The patients in this study were in general in the very latest stages of disease, yet there were many improvements, some of which were marked. However, it is generally regarded that any modality of anticancer therapy has its best chances of success when used *early* in the course of disease. And this is probably true of hydrazine sulfate. There would seemingly be no disadvantage in instituting hydrazine sulfate therapy early in the course of disease, especially in those cases where the ultimate clinical course is virtually unaffected by any known therapeutic modality. Moreover, since the toxicity of hydrazine sulfate is apparently of a low order of magnitude, unlike many of the cytotoxic drugs whose 'side effects' can produce extreme patient discomfort and death, it would seem prudent to investigate the effect of this drug on early patients, rather than use it at the very last stages as a 'resurrective' type of therapy. If

positive responses can be obtained in terminal patients – as indicated in this study – it seems only reasonable that a greater degree of positive response could be expected in early patients, as is the case with many other anticancer modalities.

Side Effects

The side effects of hydrazine sulfate are indeed of a very minor nature as reported in this study, with the possible exception of 'torpidity' or 'drowsiness' which had less than a 1 % incidence and occurred only in very advanced bedridden case(s). The most frequent side effect, occurring usually after the 6th week of therapy, appears to be the development of mild extremity paresthesias, particularly of the fingers and toes. This condition reportedly can be diminished or eliminated by dosage reduction and/or addition of vitamin B_6 (in excess of 25 mg daily) to the regimen. Other side effects such as nausea, pruritis, etc., appear to be transient in nature and not a clinical problem, with few exceptions. In general, since hydrazine sulfate is not a cytotoxic agent, there have been none of the severe side effects of these drugs reported with its use, and this is especially true of hematopoietic-suppressive effects. Hydrazine sulfate does not depress the bone marrow. On the contrary, several of the cases of this study with advanced prostatic or breast cancer showed net *elevations* in hemoglobin, hematocrit and platelets within 2 weeks of initiation of treatment. This observation has been confirmed in many case reports not a part of this study and thus is in contrast to the cytotoxic drugs, one of the prime limitations of which are their hematosuppressive effects. Finally, hydrazine sulfate has not been demonstrated clinically to possess immunosuppressive properties, although this must await verification by further basic studies.

Concluding Remark

Hydrazine sulfate therapy is a new type of chemotherapy. Its clinical use at present represents a *beginning*. Whether a study with any new drug is positive or negative, it must always be evaluated in terms of the 'state of the art'. Hydrazine sulfate represents the *first* of a class of new agents designed to interrupt host participation in cancer. Other agents in this class now in development may prove to be far superior to hydrazine sulfate. In addition, adjunctive agents to hydrazine sulfate therapy may also prove to be very important. In this respect it has already been learned by this laboratory that administration of a substance interfering with triglyceride synthesis, can greatly potentiate the anticancer action of hydrazine sulfate (paper in preparation). For these types of reasons it must be emphasized that the clinical potential of hydrazine sulfate-like drugs in cancer has only just begun to be explored, and much further work lies ahead before a more comprehensive understanding of their ultimate anticancer potential becomes clear.

References

1 *Gold, J.:* Cancer cachexia and gluconeogenesis. Ann. N.Y. Acad. Sci. *230:* 103–110 (1974).
2 *Gold, J.:* Inhibition of gluconeogenesis at the phosphoenolpyruvate carboxykinase and pyruvate carboxylase reactions, as a means of cancer chemotherapy. Oncology *29:* 74–89 (1974).
3 *Gold, J.:* Use of hydrazine sulfate in advanced cancer patients: preliminary results. Proc. Am. Ass. Cancer Res. *15:* 83 (1974).
4 *Strum, S.B.; Bierman, H.R., and Thompson, R.:* Hydrazine sulfate in patients with neoplasia. Proc. Am. Ass. Cancer Res. *16:* 243 (1975).

Joseph Gold, Syracuse Cancer Research Institute Inc., Presidential Plaza, 600 East Genesee Street, *Syracuse, NY 13202* (USA)

Oncology *32:* 11–20 (1975)

Primary C-Cell Hyper

Miroslaw Beskid

Laboratory of Histochemistr
Postgraduate Medical Educa

Key Words. Thyroid C cells · carcinoma

Abstract. The electron mic C-cell hyperplasia in 'hot' thyroid was found within nodule tissue. I is in normal thyroid tissue plays a

Introduction

It was demonstrated on methods that the so-called p the follicular cells and const gland (2, 6, 8, 19, 21, 29, exclusively restricted to neop and pathological properties ((1, 3, 9, 23–27, 31, 35, 36) recently described C-cell ad besides neoplasm the C cells hyperplasia within normal thy

Owing to the fact that hyperplasia preceding carcin microscopic properties of C such a case seems relevant.

A. INGREDIENT NAME:

METRONIDAZOLE BENZOATE

B. Chemical Name:

5-nitro-1*H*-imidazol-1-ylethyl benzoate

C. Common Name:

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

Assay: 99.54% calculated as dried basis

E. Information about how the ingredient is supplied:

White or slightly yellowish, crystalline powder

F. Information about recognition of the substance in foreign pharmacopeias:

The Indian Pharmacopeia Volume I (A-P) 1985

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Stolze, K. Elimination of Elyzol 25% Dentagel matrix from periodontal pockets. *J Clin Periodontol,* 1995; 22(3): 185-187.

H. Information about dosage forms used:

Suspension

I. Information about strength:

400mg- 3 times daily, for 5 - 10 days

J. Information about route of administration:

Topically

K. Stability data:

Melts at about 99-102°
Keep container tightly closed

L. Formulations:

M. Miscellaneous Information:

Milan, 11th December 1997

2 x 25-kg drums

30-1559
#55197

Manuf. date : July 1997
Expiry date : July 2002

ANALYSIS CERTIFICATE No. 3243

Your Ord. No. of the 10th Dec. 1997 Our Ref. No. 2925

MATERIAL METRONIDAZOLE BENZOATE B.P. micronized	Quantity	Batch
	KG. 50.-	0712

Empirical formula

Molecular weight

Aspect micronized powder

Color slig. yellowish

Odor

Taste

Melting point 99 - 102°C

Boiling range

Solubility practically insoluble in water; freely soluble in Dichloromethone; soluble in Acetone.

pH (acidity) 0.09 ML

Titer (Assay) 99.54% calculated as dried basis

Specific rotation

Light absorption

Loss on drying 0.1483%

Residue on ignition 0.0398%

Chloride

Sulfate

Heavy metals Less than 20 ppm

Identification : A) Melting 99 - 102°C
B) complies
C) -
D) Related substances pa
E) te

Other requirements, notes Results of test or analysis as per B.P.

The Analyst 12/97

QUALITY CONTROL REPORT

CHEMICAL NAME.: METRONIDAZOLE BENZOATE POWDER

MANUFACTURE LOT NO.: 0712

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP__/BP__/MERCK__/NF__/MART.__/CO.SPECS.__.

1) DESCRIPTION.:
WHITE OR SLIGHTLY CREAM TO YELLOWISH, CRYSTALLINE POWDER OR FLAKES.

2) SOLUBILITY.:
VERY SOLUBLE IN CHLOROFORM, ALCOHOL; SOLUBLE IN ETHER, INSOLUBLE IN WATER.

3) MELTING POINT.:
MELTS AT ABOUT 99-102 degree. K

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:
A) COMPLIES BY IR SPECTRUM AS PER COMPANY SPECS.
B) A SOLUTION PH IS 5.8.

PASSES.:_____ **FAILS.:**_____

COMMENTS.:

ANALYST SIGNATURE.:_____ **DATE.:**_____

PREPACK TEST.:_____ **DATE.:**_____ **INITIAL.:**_____

RETEST.:_____ **DATE.:**_____ **INITIAL.:**_____

MATERIAL SAFETY DATA SHEET

1. CHEMICAL PRODUCT IDENTIFICATION

Product name : METRONIDAZOLE BENZOATE
Chemical name : 1-(2-benzoyloxyethyl)-2-methyl-5-nitro imidazole
Emp. Formula : $C_{13}H_{13}N_3O_4$ - 275.3

2. COMPOSITION / INFORMATION ON INGREDIENTS

Chemical name	CAS N°	EINECS N°	Symbol	%
1-(2-benzoyloxyethyl)-2-methyl-5-nitro imidazole	69198-10-3		Xn	99%

3. HAZARD IDENTIFICATION

Effect(s) of (over)exposure: May cause irritation to respiratory apparatus.

Symptoms of (over)exposure

Inhalation : not available
Skin : not available
Eyes : not available
Ingestion : not available

4. FIRST AID MEASURES

Inhalation:	**Effects**	May be irritating.
	First aid	Remove victim to fresh air. Keep victim at rest. Consult a doctor.
Skin:	**Effects**	May be irritating.
	First aid	Remove contamined clothing. Wash off with plenty of water and soap. Consult a doctor.
Eyes:	**Effects**	May be irritating.
	First aid	Wash out with plenty of water. Consult a doctor.
Ingestion:	**Effects**	LD_{50} 1.050 mg/Kg
	First aid	Wash out mouth with water. Consult a doctor.

5. FIRE FIGHTING MEASURES

Extinguishing measures

Suitable	:	Water spray, CO_2, foam, dry chemical
Not be used	:	
Hazardous thermal decomposition and combustion products	:	CO, CO_2, NOx
Protective equipment	:	Self-contained breathing apparatus. Full protective clothing.

6. ACCIDENTAL RELEASE MEASURES

Personal precautions	:	Wear suitable protective clothing. When using do not eat, drink or smoke.
Environmental precautions	:	Not available.
Cleaning procedures	:	Collect spilled material. Clean up affected area with water.

See section 8 and 13

7. HANDLING AND STORAGE

Handling	:	Ventilation recommended. When using do not eat, drink or smoke.
Storage	:	Keep container tightly closed.

8. EXPOSURE CONTROLS / PERSONAL PROTECTION

Respiratory protection	:	Airlined respirator or dust mask, type P2.
Hand protection	:	Rubber gloves.
Eye protection	:	Safety goggles or face shield.
Skin protection	:	Working clothing.

Product name: METRONIDAZOLE BENZOATE

9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance	: crystalline powder	**Vapour pressure**	: Not available
Colour	: white to yellowish-white	**Vapour density**	: Not available
Odour	: odourless	**Flash point**	: Not available
Melting point	: 99° - 103°C	**Autoignition**	: Not available
Boiling point	: Not available	**Flammability**	: Not flammable
Relative density	: Not available	**Explosive properties**	: Not available
Bulk density	: Not available	**Upper limit**	: -
Solubility in water	: 0.5% at 20°C	**Lower limit**	: -
pH	: Not available	**Viscosity**	: Not available
Partition coefficient	: Not available	**Conductivity**	: Not available

10. STABILITY AND REACTIVITY

Conditions to avoid : -

Materials to avoid : Oxidizing agents

Hazardous decomposition products : NOx

11. TOXICOLOGICAL INFORMATION

Acute toxicity

- **Oral** : Not available
- **Dermal** : Not available
- **Inhalation** : May be irritating

Eye irritation : May be irritating

Skin irritation : May be irritating

Other information : Not available

12. ECOLOGICAL INFORMATION

Mobility : Not available

Persistence and degradability : Not available

Bioaccumulative potential : Not available

Ecotoxicity : Not available

13. DISPOSAL CONSIDERATIONS

Methods of disposal : Combustion in an incinerator for chemical waste.

Danger(s) : Not available

14. TRANSPORT INFORMATION

Special precautions :

Classification

UN Code :
ADR/RID :
IMO :
Packaging group :
ICAO/IATA :

15. REGULATORY INFORMATION

EC Classification

Contains: 1-(2-benzoyloxyethyl)-2-methyl-5-nitro imidazole

Symbol: Xn

Risk phrases: 20/22

Safety phrases: 2

16. OTHER INFORMATION

The information contained in this data sheet is, to the best of our knowledge, true and accurate, but any recommendations or suggestions which may be made are without guarantee, since the conditions of use are beyond our control.
Furthermore, nothing contained herein shall be construed as a recommendation to use any product in conflict with existing patents covering any material or its use.

Issued on January 1998

Storage Store in a well-closed container, protected from light.

Preparation

Methylprednisolone Acetate Injection

Action and use Corticosteroid.

1/95

Metoprolol Tartrate

Identification Test A. Line 4. For '18°' read '−18°'.

Line 6. After 'residue' insert ', Appendix II A'.

12/93

Heavy metals Line 2. For '1 ml' read '10 ml'.

7/94

Add the following statement.

Preparations

Metoprolol Injection

Metoprolol Tartrate Tablets

Metronidazole

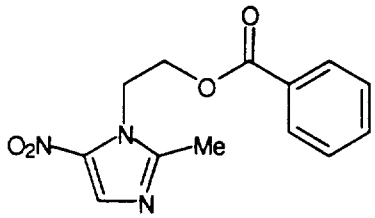
Add a five-pointed star (☆) to the title.

7/94

Preparations Add the following:

Metronidazole Intravenous Infusion

Metronidazole Benzoate ☆



$C_{13}H_{13}N_3O_4$ 275.3 *13182-89-3*

Definition Metronidazole Benzoate contains not less than 98.5% and not more than 101.0% of 2-(2-methyl-5-nitro-1*H*-imidazol-1-ylethyl benzoate, $C_{13}H_{13}N_3O_4$, calculated with reference to the dried substance.

Characteristics White or slightly yellowish, crystalline powder or flakes; practically insoluble in *water*, freely soluble in *dichloromethane*; soluble in *acetone*; slightly soluble in *ethanol (96%)*; very slightly soluble in *ether*.

Identification *Identification test C may be omitted if identification tests A, B, D and E are carried out. Identification tests B, D and E may be omitted if identification tests A and C are carried out.*

A. *Melting point*, 99° to 102°, Appendix V A, Method I.

B. Dissolve 0.1 g in 1M *hydrochloric acid* and dilute to 100 ml with the same acid. Dilute 1 ml of the solution to 100 ml with 1M *hydrochloric acid*. Examined between 220 nm and 350 nm, Appendix II B, the solution shows two absorption maxima, at 232 nm and 275 nm. The *specific absorbance* at the maximum at 232 nm is 525 to 575.

C. Examine by *infrared absorption spectrophotometry*, Appendix II A. The absorption maxima in the spectrum obtained with the substance being examined correspond in position and relative intensity to those in the spectrum obtained with *metronidazole benzoate EPCRS*.

D. Examine the chromatograms obtained in the test for Related substances under *ultraviolet light (254 nm)*. The principal spot in the chromatogram obtained with solution (2) is similar in position and size to the principal spot in the chromatogram obtained with solution (3).

E. To about 10 mg add about 10 mg of *zinc powder*, 1 ml of *water* and 0.3 ml of *hydrochloric acid*. Heat on a water bath for 5 minutes and cool. The solution yields the reaction characteristic of *primary aromatic amines*, Appendix VI.

Appearance of solution Dissolve 1 g in *dimethylformamide* and dilute to 10 ml with the same solvent. The solution is not more opalescent than *reference suspension II*, Appendix IV A, and not more intensely coloured than *reference solution* GY_3, Appendix IV B, Method II.

Acidity Dissolve 2 g in a mixture of 20 ml of *dimethylformamide* and 20 ml of *water*, previously neutralised with 0.02M *hydrochloric acid VS* or 0.02M *sodium hydroxide VS* using 0.2 ml of *methyl red solution*. Not more than 0.25 ml of 0.02M *sodium hydroxide VS* is required to change the colour of the indicator.

Related substances Examine by *thin-layer chromatography*, Appendix III A, using *silica gel* HF_{254} as the coating substance. Heat the plate at 110° for 1 hour and allow to cool before use.

Solution (1) Dissolve 0.20 g of the substance being examined in *acetone* and dilute to 10 ml with the same solvent.

Solution (2) Dilute 1 ml of solution (1) to 10 ml with *acetone*.

Solution (3) Dissolve 20 mg of *metronidazole benzoate EPCRS* in *acetone* and dilute to 10 ml with the same solvent.

Solution (4) Dilute 5 ml of solution (2) to 100 ml with *acetone*.

Solution (5) Dilute 2 ml of solution (2) to 100 ml with *acetone*.

Solution (6) Dissolve 10 mg of *metronidazole EPCRS* in *acetone* and dilute to 100 ml with the same solvent.

Solution (7) Dissolve 10 mg of *2-methyl-5-nitroimidazole* in *acetone* and dilute to 100 ml with the same solvent.

Solution (8) Dissolve 10 mg of *metronidazole EPCRS* and 10 mg of *2-methyl-5-nitroimidazole* in *acetone* and dilute to 50 ml with the same solvent.

Apply separately to the plate 10 µl of each solution. Develop over a path of 15 cm using *ethyl acetate*. Allow the plate to dry in air and examine under *ultraviolet light (254 nm)*. In the chromatogram obtained with solution (1) any spot corresponding to metronidazole or 2-methyl-5-nitroimidazole is not more intense than the corresponding spot in the chromatograms obtained with solutions (6) and (7) respectively (0.5%). Any other *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (4) (0.5%) and at most one such spot is more intense than the spot in the chromatogram

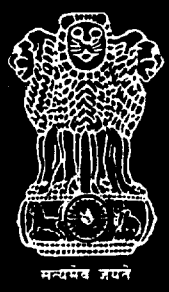
Ministry of Health & Family Welfare

Pharmacopoeia of India

(The Indian Pharmacopoeia)

Volume – I
(A – P)

Third Edition



PUBLISHED BY THE CONTROLLER OF PUBLICATIONS, DELHI

1985

Loss on drying : Not more than 0.5 per cent, determined on 1.0 g by drying in an oven at 105°, Appendix 5.8.

Assay : Weigh accurately about 0.45 g and dissolve in 10 ml of *glacial acetic acid*, add a few drops of *1-naphthol-benzein solution* and titrate with *0.1N perchloric acid* until a pale-green colour is produced. Perform a blank determination and make any necessary correction. Each ml of *0.1N perchloric acid* is equivalent to 0.01712 g of $C_6H_9N_3O_3$.

Storage : Store in well-closed light-resistant containers.

Metronidazole Tablets

Category : Anti-amoebic; antitrichomonal; antigiardial.

Dose : Metronidazole. For trichomoniasis, 200 mg three times daily, for 7 days.

For amoebiasis, 400 mg three times daily, for 8 to 10 days.

For giardiasis, 2 g daily for three successive days for adults, 1 g daily for children and 400 mg daily for infants.

Usual strengths : 200 mg; 400 mg.

Standards : Metronidazole Tablets contain not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of Metronidazole, $C_6H_9N_3O_3$. The tablets may be coated.

Identification : (A) Shake a quantity of the powdered tablets equivalent to about 0.2 g of Metronidazole with 4 ml of *N sulphuric acid* and filter. To the filtrate add 10 ml of *picric acid solution* and alow to stand for one hour, the precipitate after washing with cold *water* under suction and drying at 105° melts at about 150°, Appendix 5.11.

(B) Comply with **Identification** test (B) described under Metronidazole, using a quantity of the powdered tablets equivalent to 10 mg of Metronidazole.

2-Methyl-5-nitroimidazole : Comply with the test described under Metronidazole, using as solution (1), a solution prepared in the following manner: Shake a quantity of the powdered tablets equivalent to 0.2 g of Metronidazole with 5 ml of mixture of equal volumes of *chloroform* and *methyl alcohol* for five minutes and filter. The chromatogram obtained with solution (1) may also show spots due to excipients.

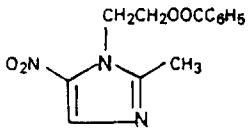
Other requirements : Comply with the requirements stated under Tablets.

Assay : Weigh and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to 0.2 g of Metronidazole, transfer to a sintered-glass crucible and extract with six quantities, each of 10 ml, of hot *acetone*. Cool, add to the combined extracts 50 ml of *acetic anhydride*, 0.1 ml of a 1 per cent w/v solution of *brilliant green* in *glacial acetic acid* and titrate with *0.1N perchloric acid* to a yellowish-green end-point. Perform a blank determination and make any necessary correction. Each ml of *0.1N perchloric acid* is equivalent to 0.01712 g of $C_6H_9N_3O_3$.

Storage : Store in well-closed, light-resistant containers.

Metronidazole Benzoate

Benzoyl Metronidazole



$C_{13}H_{13}N_3O_4$ Mol. Wt. 275.27

Category : Anti-amoebic.

Dose : For amoebic dysentry, the equivalent of 400 mg of metronidazole three times, daily, for 5 to 10 days.

NOTE – 200 mg of Metronidazole Benzoate is approximately equivalent to 125 mg of metronidazole.

Description : White or cream-coloured crystalline powder, odourless; almost tasteless.

Solubility : Sparingly soluble in *water*; soluble in *chloroform*, in *acetone*, and in *alcohol (90 per cent)*.

Standards : Metronidazole Benzoate is 2-(2-methyl-5-nitro-imidazol-1-yl) ethyl benzoate. It contains not less than 98.0 per cent of $C_{13}H_{13}N_3O_4$, calculated with reference to the dried substance.

Identification : (A) The light absorption, in the range 230 to 530 nm of a 1-cm layer of a 0.001 per cent w/v solution in *ethyl alcohol* exhibits a maximum only at 309 nm; *extinction* at 309 nm, about 0.3, Appendix 5.15 A.

(B) It gives the reactions of *benzoates*, Appendix 3.1.

Melting range : Between 100° and 102°, Appendix 5.11.

pH : Between 5.0 and 7.0, determined in a 2.0 per cent w/v suspension, Appendix 5.10.

Free benzoic acid : Not more than 0.2 per cent, determined by the following method: Dissolve 0.50 g in 25 ml of *alcohol* and titrate with *0.1N sodium hydroxide*, using *phenol red solution* as indicator. Perform a blank determination and make any necessary correction. Each ml of

0.1N sodium hydroxide is equivalent to 0.01221 g of $C_7H_6O_2$.

Related substances : Carry out the method for *thin-layer chromatography*, Appendix 5.4.3, using *silica gel HF 254* as the coating substance and a mixture of 8 volumes of *chloroform* and 2 volumes of *acetone* as the mobile phase. Apply separately to the plate 10 µl of each of three solutions in a mixture of equal volumes of *methyl alcohol* and *chloroform* containing (1) 6.0 per cent w/v of the substance being examined; (2) 0.02 per cent w/v of *2-methyl-5-nitroimidazole R.S.* and; (3) 0.02 per cent w/v of *metronidazole R.S.* After removal of the plate, allow the solvent to evaporate and examine under an ultra-violet lamp having a maximum output at about 254 nm. The spots in the chromatogram obtained with solutions (2) and (3) are more intense than any corresponding spots in the chromatogram obtained with solution (1).

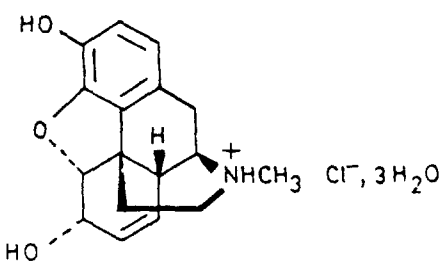
Sulphated ash : Not more than 0.1 per cent, Appendix 3.2.7.

Loss on drying : Not more than 0.5 per cent, determined on 1.0 g by drying "in vacuo at 60°," Appendix 5.8.

Assay : Weigh accurately about 0.5 g and dissolve in 50 ml of *acetone*. Add 10 ml of *acetic anhydride* and titrate with *0.1N perchloric acid* using *brilliant green solution* as indicator. Perform a blank determination and make any necessary correction. Each ml of *0.1N perchloric acid* is equivalent to 0.02753 g of $C_{13}H_{13}N_3O_4$.

Storage : Store in well-closed, light-resistant containers.

Morphine Hydrochloride



$C_{17}H_{19}NO_3, HCl, 3H_2O$ Mol. Wt. 375.85

Category : Narcotic, analgesic.

Dose : 10 to 20 mg.

Description : Colourless, glistening needles or white crystalline powder; odourless; taste, bitter.

Solubility : Soluble in *water*; sparingly soluble in *alcohol*; practically insoluble in *solvent ether* and in *chloroform*; soluble in *glycerin*.

Standards : Morphine Hydrochloride is the trihydrate of the hydrochloride of 7,8-didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol, which may be obtained from opium. It contains not less than 98.0 per cent and not more than the equivalent of 100.5 per cent of $C_{17}H_{19}NO_3, HCl$, calculated with reference to the dried substance.

Identification : (A) Sprinkle a small quantity in powder form on the surface of a drop of *nitric acid*; an orange-red colour is produced.

(B) To a 2 per cent w/v solution add *potassium ferricyanide solution* containing 1 drop per ml of *ferric chloride test-solution*; an immediate bluish-green colour is produced (distinction from codeine).

(C) Add 5 ml of *sulphuric acid* to 5 mg in a test-tube, and add 1 drop of *ferric chloride test solution*, and heat in boiling water for two minutes; a deep blue colour is produced. Add a drop of *nitric acid*; the colour changes to dark red-brown (codeine and ethylmorphine give the same colour reactions, but dihydromorphine and papaverine do not produce this colour change).

(D) Add to about 1 mg of the powdered substance in a porcelain dish 0.5 ml of *sulphuric acid* containing 1 drop of *formaldehyde solution*. A purple colour is formed which turns to violet.

(E) Dissolve about 5 mg in 5 ml of *water*, and add 1 ml of *hydrogen peroxide solution*, 1 ml of *dilute ammonia solution* and 1 drop of a 4 per cent w/v solution of *copper sulphate*. A transient red colour develops.

(F) A solution (1 in 20) gives the reactions of *chlorides*, Appendix 3.1.

Acidity or Alkalinity : Dissolve 0.2 g in 10 ml of freshly boiled and cooled *water* add 1 drop of *methyl red solution*. Not more than either 0.2 ml of *0.02N sodium hydroxide* or of *0.02N hydrochloric acid* is required to change the colour of the solution.

Specific optical rotation : Between −112° and −115°, calculated with reference to the dried substance and determined in a 2 per cent w/v solution, Appendix 5.12.

Ammonium salts : Heat 0.2 g with *sodium hydroxide solution* on a water-bath for one minute; no odour of ammonia is perceptible.

Other alkaloids : Not more than 1.5 per cent, calculated with reference to the dried substance, determined by the following method: Transfer 0.5 g to a separator, add 15 ml of *water*, 5 ml of *N sodium hydroxide*, and 10 ml of *chloroform*, shake, allow to separate, and transfer the chloroform solution to another separator. Repeat the extraction with two further quantities, each of 10 ml, of *chloroform*. Wash the mixed chloroform solutions with 10 ml of *0.1N sodium hydroxide* and then with two successive quantities, each of 5 ml, of *water*, evaporate to dryness on a water-bath, and dry the residue to constant weight at 105°.

National Library of Medicine: IGM Full Record Screen

TITLE: Elimination of Elyzol 25% Dentalgel matrix from periodontal pockets.

AUTHOR: Stoltze K

AUTHOR AFFILIATION: Department of Periodontology, School of Dentistry, Faculty of Health Sciences, University of Copenhagen, Denmark.

SOURCE: J Clin Periodontol 1995 Mar;22(3):185-7

NLM CIT. ID: 95310528

ABSTRACT: Elyzo 25% Dentalgel (EDG) which is developed for use in the treatment of periodontitis is a suspension of metronidazole benzoate (40%) in a mixture of glyceryl mono-oleate (GMO) and triglyceride (sesame oil). Metronidazole can be detected in the periodontal pockets 24-36 h after application. The aim of the present study was to estimate the period of time that the gel matrix persists on periodontal pockets after 1 application of EDG. 12 patients were included in the study. From each patient, 1 sample was taken before and immediately after, and 1, 2, 3, 4, 5, 6, 8, 12 and 24 h after application. Subgingival scaling followed by absorption of gingival crevicular fluid with filter paper was used for sampling. The sampling unit was 1 tooth. Each sample was assayed for the amount of GMO and oleic acid (a degradation product of GMO) by means of high-performance liquid chromatography (HPLC) with UV detection. To allow determination of the GMO dose applied into the pockets and to estimate the recovery rate of the sampling method, 1 tooth in each patient was selected for sampling as soon as the gel had set, i.e., about 10 min after application. Only in 1 patient was a detectable amount of GMO within the pocket revealed 24 h after application. This amount was approximately 0.5% of the mean GMO dose applied around 1 tooth. GMO was found no longer than 12 h in the remaining patients.

MAIN MESH SUBJECTS: Glycerides/ADMINISTRATION & DOSAGE/ANALYSIS/*PHARMACOKINETICS
Metronidazole/*ANALOGS & DERIVATIVES/ADMINISTRATION & DOSAGE/ ANALYSIS/*PHARMACOKINETICS
Periodontal Pocket/*METABOLISM
Sesame Oil/ADMINISTRATION & DOSAGE/ANALYSIS/*PHARMACOKINETICS

A. INGREDIENT NAME:

PENTYLENE TETRAZOLE

B. Chemical Name:

1,5-Pentamethylenetetrazole, 6,7,8,9-Tetrahydro-5H-tetrazoloazepine

C. Common Name:

Leptazol Injection Giazol, Angioton, Angiotonin, Cardiazol, Cardiazole, Cardifortan, Cardiol, Cardiotonicum, Cardosal, Cordosan, Cenalene-M, Cenazol, Centrazole, Cerebro-Nicin, Coranormal, Coranormol, Corasol, Coratoline, Corazol, Corazole, Corazole (Analeptic) Corisan, Corsedrol, Cortis, Corvasol, Corvis, Coryvet.

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

	(Minimum)	*(Resuslt)*
Assay	98%	99.80%

E. Information about how the ingredient is supplied:

White crystals, slightly pungent and bitter, very stable, not easily attacked by other substances.

F. Information about recognition of the substance in foreign pharmacopeias:

Aust., Cz., Hung., It., Arg., Belg., Br., Eur., Fr., Ger., Hung., Ind., Int., It., Jug., Mex., Neth., Nord., Pol., Port., Rus., Span., Swiss., and Turk.

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Jun, H. W. Absorption and Fate. *J. Pharm. Sci.*, 1975;64:1843.

Khazi, I. A., Mahajanshetti, C. S., and Gadad A. K. Pentylene tetrazole induced convulsions. *Arzneimittelforschung*, 1996;46(10):949-952.

Erol, D. D., Calis, U., and Demirdamar, R. Pentylene tetrazole-induced seizures in mice. *J. Pharm. Sci.* 1995; 84(4):462-465

H. Information about dosage forms used:

Orally
Injection

I. Information about strength:

100-200mg

J. Information about route of administration:

Given by mouth

K. Stability data:

Melts at about 57-60°

L. Formulations:

Leptazol is a sterile solution of pentetrazol 10% and sodium phosphate 0.25% in water for injections, adjusted to pH 7.8 with dilute hydrochloric acid or potassium hydroxide solution.

M. Miscellaneous Information:

CERTIFICATE OF ANALYSIS

30-1103
#53751

Date: 10/15/97

Page 1

PRODUCT: PENTYLENETETRAZOLE - A

CATALOG NO: PE104 **
LOT NO: MJ0251

DESCRIPTION	LIMIT MIN.	LIMIT MAX.	RESULT
ASSAY	98 %	-	99.80 % D
MELTING RANGE	59 - 61 C		59 - 61 C

✓

APPROVED BY: Lilian D. Casabar
LILIAN D. CASABAR

10/97

QUALITY CONTROL REPORT

CHEMICAL NAME.: PENTYLENETETRAZOLE _____

MANUFACTURE LOT NO.: MJ0251

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP__/BP__/MERCK__/NF__/MART.__/CO.SPECS.__.

1) DESCRIPTION.:
WHITE CRYSTALS, SLIGHTLY PUNGENT AND BITTER; VERY STABLE, NOT EASILY ATTACKED BY OTHER SUBSTANCES.

2) SOLUBILITY.:
FREELY SOLUBLE IN WATER AND IN MOST ORGANIC SOLVENTS. SLIGHTLY SOLUBLE IN ALCOHOL.

3) MELTING POINT.:
MELTS AT ABOUT 57-60 DEGREES.

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:

PASSES.: _____ **FAILS.:** _____

COMMENTS.:

ANALYST SIGNATURE.: _____ **DATE.:** _____

PREPACK TEST.: _____ **DATE.:** _____ **INITIAL.:** _____

RETEST.: _____ **DATE.:** _____ **INITIAL.:** _____

---------- IDENTIFICATION ----------

PRODUCT #: P720-7 NAME: 1,5-PENTAMETHYLENETETRAZOLE, 98%

CAS #: 54-95-5

MF: C6H10N4

SYNONYMS

ANGIAZOL * ANGIOTON * ANGIOTONIN * CARDIAZOL * CARDIAZOLE * CARDIFORTAN * CARDIOL * CARDIOTONICUM * CARDOSAL * CARDOSAN * CENALENE-M * CENAZOL * CENTRAZOLE * CEREBRO-NICIN * CORANORMAL * CORANORMOL * CORASOL * CORATOLINE * CORAZOL * CORAZOLE * CORAZOLE (ANALEPTIC) * CORISAN * CORSEDROL * CORTIS * CORVASOL * CORVIS * CORYVET * ALPHA,BETA-CYCLOPENTAMETHYLENETETRAZOLE * DEAMOCARD * DELZOL-W * DIOVASCOLE * DEUMACARD * GEWAZOL * KARDIAZOL * KORAZOL * KORAZOLE * LEPAZOL * LEPTAZOL * LEPTAZOLE * METRAZOL * METRAZOLE * NAURANZOL * NAURAZOL * NEDCARDOL * NEOCARDOL * NEURAZOL * NOVO CORA- VINCO * OPTICOR * PEMETESAN * PENETRASOL * PENETRATSOL * PENETIAZOL * PENTACARD * PENTACOR * PENTAMETHAZOL * PENTAMETHAZOLUM * PENTAMETHYLENETETRAZAL * PENTAMETHYLENETETRAZOL * PENTAMETHYLENETETRAZOLE * PENTAMETHYLENE-1,5-TETRAZOLE * 1,5- PENTAMETHYLENETETRAZOLE * PENTAMETILENTETRAZOLO (ITALIAN) * PENTAZOL * PENTAZOLUM * PENTEMESAN * PENTETRAZOL * PENTETRAZOLE * PENTRAZOL * PENTROLONE * PENTROZOL * PENTYLENETETRAZOL * PENTYLENETETRAZOLE * PETAZOL * PETEZOL * PETRAZOLE * PHRENAZOL * PHRENAZONE * PMT * PTZ * STELLACARDIOL * STILLCARDIOL * TETRACOR * 6,7,8,9-TETRAHYDRO-5-AZEPOTETRAZOLE * 6,7,8,9-TETRAHYDRO-5H-TETRAZOLOAZEPINE * 7,8,9,10- TETRAZABICYCLO(5.3.0)-8,10-DECADIENE * 1,2,3,3A-TETRAZACYCLOHEPTA-8A, 2-CYCLOPENTADIENE * TETRASOL * TETRAZOL * TETRAZOLE, PENTAMETHYLENE- * 5H-TETRAZOLO(1,5-A)AZEPINE, 6,7,8,9-TETRAHYDRO- (8CI,9CI) * TT87 * VASAZOL * VASOREX * VENTRAZOL * YETRAZOL *

---------- TOXICITY HAZARDS ----------

RTECS NO: XF8225000

5H-TETRAZOLOAZEPINE, 6,7,8,9-TETRAHYDRO-

TOXICITY DATA

ORL-MAN LDLO:147 MG/KG	85DCAI 2,73,70
IVN-MAN LDLO:29 MG/KG	85DCAI 2,73,70
ORL-RAT LD50:140 MG/KG	JPPMAB 13,244,61
IPR-RAT LD50:62 MG/KG	TXAPA9 18,185,71
SCU-RAT LD50:85 MG/KG	TXAPA9 18,185,71
IVN-RAT LD50:45 MG/KG	AIPTAK 135,9,62
REC-RAT LD50:8 MG/KG	AACRAT 46,395,67
ORL-MUS LD50:88 MG/KG	JPETAB 128,176,60
IPR-MUS LD50:55 MG/KG	AIPTAK 123,419,60
SCU-MUS LD50:70 MG/KG	BCFAAI 111,293,72
IVN-MUS LD50:31400 UG/KG	AIPTAK 103,146,55
PAR-MUS LD50:72 MG/KG	ARZNAD 6,583,56
SCU-RBT LD50:76 MG/KG	JAPMA8 29,2,40
IVN-RBT LD50:30 MG/KG	PHTXA6 21,1,58
SCU-FRG LD50:1600 MG/KG	PLRCAT 1,7,69

REVIEWS, STANDARDS, AND REGULATIONS

NOHS 1974: HZD 84704; NIS 1; TNF 68; NOS 6; TNE 2770

EPA TSCA CHEMICAL INVENTORY, JUNE 1990

TARGET ORGAN DATA

BRAIN AND COVERINGS (RECORDINGS FROM SPECIFIC AREAS OF CNS)

BEHAVIORAL (TREMOR)

BEHAVIORAL (CONVULSIONS OR EFFECT ON SEIZURE THRESHOLD)

BEHAVIORAL (EXCITEMENT)

BEHAVIORAL (MUSCLE CONTRACTION OR SPASTICITY)

LUNGS, THORAX OR RESPIRATION (OTHER CHANGES)

ONLY SELECTED REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES (RTECS)

DATA IS PRESENTED HERE. SEE ACTUAL ENTRY IN RTECS FOR COMPLETE INFORMATION.

---------- HEALTH HAZARD DATA ----------

ACUTE EFFECTS

HARMFUL IF SWALLOWED, INHALED, OR ABSORBED THROUGH SKIN.

MAY CAUSE IRRITATION.

EXPOSURE CAN CAUSE:

CNS STIMULATION

CONVULSIONS

TARGET ORGAN(S):

CENTRAL NERVOUS SYSTEM

FIRST AID

IN CASE OF CONTACT, IMMEDIATELY FLUSH EYES OR SKIN WITH COPIOUS

CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER

OBSERVE ALL FEDERAL, STATE, AND LOCAL LAWS.

--- PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE ---

WEAR APPROPRIATE NIOSH/MSHA-APPROVED RESPIRATOR, CHEMICAL-RESISTANT GLOVES, SAFETY GOGGLES, OTHER PROTECTIVE CLOTHING.

SAFETY SHOWER AND EYE BATH.

USE ONLY IN A CHEMICAL FUME HOOD.

DO NOT BREATHE DUST.

AVOID CONTACT WITH EYES, SKIN AND CLOTHING.

AVOID PROLONGED OR REPEATED EXPOSURE.

WASH THOROUGHLY AFTER HANDLING.

TOXIC.

KEEP TIGHTLY CLOSED.

STORE IN A COOL DRY PLACE.

TOXIC BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.

IF YOU FEEL UNWELL, SEEK MEDICAL ADVICE (SHOW THE LABEL WHERE POSSIBLE).

WEAR SUITABLE PROTECTIVE CLOTHING, GLOVES AND EYE/FACE PROTECTION.

TARGET ORGAN(S):

NERVES

rations

preparations are listed below; details are given in Part 3.

Preparations

Nikethamide Injection.

ary Preparations

e Glucose; Coramine†; *Spain:* Cora†; Coramina†; e†.

ient preparations. *Ger.:* Antiadipositum X-112†; Neo; Herzfluid†; Hypotonin forte†; Poikiloton†; *Spain:* dina†; Tosidrin; *Switz.:* Gly-Coramine.

Vomica (538-h)

Neuz Vómica; Noce Vomica; Noix Vomique; emen.

57-57-3 *(anhydrous brucine).*

oeias. In *Aust., Chin., Cz., Fr., Hung., Jpn,* and *Swiss.* also include Powdered Nux Vomica.

allows *Strychnos pierriana.*

ipe seeds of *Strychnos nux-vomica* (Loganiaceae).

omica has the actions of strychnine (see Extracts of nux vomica have been used for variety of disorders including those of digesdebility.

as containing strychnine, nux vomica conicine which has similar properties.

omica (Nux vom.) is used in herbal and hopathic medicine. Ignatia, the dried seed of *hnos ignatii*, is also used in homoeopathic cine where it is known as Ignatia amara or Ia-

parations

preparations are listed below; details are given in Part 3.

etary Preparations

ingredient preparations. *Belg.:* Aperop; Digestobiase†; ; *Fr.:* Climaxol; Crème Rap; Curoveinyl; Digestobiase; Grez Chlorhydropepsique; Phosma-Hématoporphyrine†; Pink†; Quintonine; YSE; YSE Glutamique; *Ital.:* Amaro olit; Enteroton Digestivo†; Gastro-Pepsin; Lassatina; Pillole *S.Afr.:* Peter Pote's; *Spain:* Alofedina; *Switz.:* Padma-Lax.

moline (1436-b)

(BAN, USAN, rINN).

56; NSC-25159; Phenoxazole; Phenylisohydantoin; Phedohydantoin. 2-Imino-5-phenyl-4-oxazolidinone.

N_2O_2 = 176.2.

2152-34-3 (pemoline); 68942-31-4 (pemoline hydroide); 18968-99-5 (magnesium pemoline).

verse Effects, Treatment, and Precau-ns

for Dexamphetamine Sulphate, p.1547; howev- effects of over-stimulation and sympathomi- activity are considered to be less with moline. There have been reports of impaired liver ction in patients taking pemoline; its use is con- indicated in patients with liver disorders. There also been rare or isolated repor chorea, mania, and neutropenia.

se. Paranoid psychosis was o -year-old taking pemoline 75 to 225 mg d nt's com- ve use of the drug, development pressive awal syndrome, and inability t ated de- dence and it was evident that the pa icted to moline.

chert SE, Morse RM. Pemoline abuse. *J* 254:

cts on growth. Results of a study in 2 netic dren suggested that growth suppression w ntial effect of prolonged treatment with clinical tive of pemoline and that this effect might be dos d.[1] also under Dexamphetamine Sulphate, p.1548.

kinson LC, *et al.* Impaired growth in hyperkinetic c iving pemoline. *J Pediatr* 1979; **94**: 538–41.

cts on the liver. Of children taking pemoline fo % had elevated concentrations of serum as sferase (SGOT) and serum alanine amino GPT); the effect was stated to be transient a

hepatitis was associated with pemoline in a 10-yea liver enzyme values fell to normal after withdra nge with lower doses did not increase the enz ggesting a toxic threshold. Close attention to he

mbol † denotes a preparation no longer actively ed

function during the first few weeks of pemoline therapy was considered essential and it was recommended that serum enzymes should be measured at no less than every 2 weeks for the first 6 weeks and then every other month.

1. Anonymous. 'Hyperkinesis' can have many causes, symptoms. *JAMA* 1975; **232**: 1204–16.
2. Patterson JF. Hepatitis associated with pemoline. *South Med J* 1984; **77**: 938.

Effects on muscle. See under Effects on the Nervous System, p.1555.

Effects on the nervous system. Choreoathetosis and rhabdomyolysis developed in a patient following a marked increase in intake of pemoline.[1] Abnormal movements responded to diazepam.

For a discussion on central stimulants provoking Tourette's syndrome, see Dexamphetamine Sulphate, p.1548.

1. Briscoe JG, *et al.* Pemoline-induced choreoathetosis and rhabdomyolysis. *Med Toxicol* 1988; **3**: 72–6.

Effects on the prostate. Experience in one patient suggested that pemoline might adversely affect the prostate gland or interfere with tests for prostatic acid phosphatase used in the diagnosis of prostatic carcinoma.[1]

1. Lindau W, de Girolami E. Pemoline and the prostate. *Lancet* 1986; **i**: 738.

Pharmacokinetics

Pemoline is readily absorbed from the gastro-intestinal tract. About 50% is bound to plasma protein. It is partially metabolised in the liver and excreted in the urine as unchanged pemoline and metabolites.

It has been suggested that magnesium hydroxide might increase the absorption of pemoline. Pemoline with magnesium hydroxide is known as magnesium pemoline.

References.

1. Vermeulen NPE, *et al.* Pharmacokinetics of pemoline in plasma, saliva and urine following oral administration. *Br J Clin Pharmacol* 1979; **8**: 459–63.
2. Sallee F, *et al.* Oral pemoline kinetics in hyperactive children. *Clin Pharmacol Ther* 1985; **37**: 606–9.
3. Collier CP, *et al.* Pemoline pharmacokinetics and long term therapy in children with attention deficit disorder and hyperactivity. *Clin Pharmacokinet* 1985; **10**: 269–78.

Uses and Administration

Pemoline has similar actions to dexamphetamine (see p.1548) and is used as an alternative to dexamphetamine or methylphenidate in the management of hyperactivity disorders in children (see p.1544). In the UK the initial dose by mouth in such children is 20 mg each morning, increased by 20 mg at weekly intervals to 60 mg. If no improvement occurs the dose can be gradually increased to a maximum of 120 mg each morning. In the USA 37.5 mg is given each morning initially, increased gradually at weekly intervals by 18.75 mg; the usual range is 56.25 to 75 mg daily and the maximum recommended daily dose is 112.5 mg.

Pemoline is also an ingredient of an oral preparation, also containing yohimbine hydrochloride and methyltestosterone, which is given with the intention of managing failure of sexual desire and functioning in males and females.

Pemoline has been given with magnesium hydroxide (magnesium pemoline) in an attempt to increase its absorption.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Canad.: Cylert; *Ger.:* Senior; Tradon; *S.Afr.:* Dynalert; *Switz.:* Stimul; *UK:* Volital; *USA:* Cylert.

Multi-ingredient preparations. *Ger.:* Cephalo-Teknosal†; *Ital.:* Deadyn; *S.Afr.:* Lentogesic; *Spain:* Neurocordin; *UK:* Prowess.

Pentetrazol (1437-v)

Pentetrazol *(BAN, rINN).*

Corazol; Leptazol; Pentamethazol; 1,5-Pentamethylenetetrazole; Pentazol; Pentetrazolum; Pentylenetetrazol. 6,7,8,9-Tetrahydro-5*H*-tetrazoloazepine.

$C_6H_{10}N_4$ = 138.2.

CAS — 54-95-5.

Pharmacopoeias. In *Aust., Cz., Hung.,* and *It.*

Pentetrazol is a central and respiratory stimulant similar to doxapram hydrochloride (see p.1550). It has been used in respiratory depression but when respiratory stimulants are indicated other agents are generally preferred. It has also been included in multi-ingredient preparations intended for the treatment of respiratory-tract disorders including cough, cardiovascular disorders including hypotension, and for the treatment of pruritus.

Administration has been by mouth and by injection.

Porphyria. Pentetrazol has been associated with acute attacks of porphyria and is considered unsafe in patients with acute porphyria.[1]

1. Moore MR, McColl KEL. *Porphyria: drug lists.* Glasgow: Porphyria Research Unit, University of Glasgow, 1991.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Spain: Cardiorapide.

Multi-ingredient preparations. *Fr.:* Désintex-Pentazol†; *Ger.:* Cardaminol†; Jasivita†; Poikiloton†; Sympatocard†; *Ital.:* Cardiazol-Paracodina; *Spain:* Cardiorapide Efed; Espectona Compositum; Fluidin Infantil†.

Phenbutrazate Hydrochloride

(1485-y)

Phenbutrazate Hydrochloride *(BANM).*

Fenbutrazate Hydrochloride *(rINNM);* R-381. 2-(3-Methyl-2-phenylmorpholino)ethyl 2-phenylbutyrate hydrochloride.

$C_{23}H_{29}NO_3.HCl$ = 403.9.

CAS — 4378-36-3 (phenbutrazate); 6474-85-7 (phenbutrazate hydrochloride).

Phenbutrazate hydrochloride was formerly used as an anorectic agent.

Phendimetrazine Tartrate (1486-j)

Phendimetrazine Tartrate *(BANM, rINNM).*

Phendimetrazine Acid Tartrate; Phendimetrazine Bitartrate. (+)-3,4-Dimethyl-2-phenylmorpholine hydrogen tartrate.

$C_{12}H_{17}NO.C_4H_6O_6$ = 341.4.

CAS — 634-03-7 (phendimetrazine); 7635-51-0 (phendimetrazine hydrochloride); 50-58-8 (phendimetrazine tartrate).

Pharmacopoeias. In *US.*

A white odourless crystalline powder. Freely **soluble** in water; sparingly soluble in warm alcohol; practically insoluble in acetone, in chloroform, and in ether. A 2.5% solution in water has a pH of 3 to 4. **Store** in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Dexamphetamine Sulphate, p.1547.

Pharmacokinetics

Phendimetrazine tartrate is readily absorbed from the gastro-intestinal tract and is excreted in the urine, partly unchanged and partly as metabolites, including phenmetrazine.

Uses and Administration

Phendimetrazine tartrate is a sympathomimetic agent with the actions of dexamphetamine (see p.1548). It is used as an anorectic and is administered by mouth as an adjunct to dietary measures in the short-term treatment of moderate to severe obesity. The use of adjuncts in the management of obesity is discussed on p.1544 where the use of stimulant anorectics such as phendimetrazine is questioned. The usual dose is 35 mg two or three times daily 1 hour before meals, but doses should be individualised and in some cases 17.5 mg twice daily may be adequate; the dose should not exceed 70 mg three times daily. An alternative dose is 105 mg once daily in the morning as a sustained-release preparation.

Phendimetrazine hydrochloride is used similarly; it is given by mouth in doses of 15 to 40 mg daily.

1437-v

Pentetrazol *(B.P., Eur. P.).* Leptazol; Pentazol; Pentamethazol; Pentylenetetrazol; Pentetrazolum; Corazol; 1,5-Pentamethylenetetrazole. 6,7,8,9-Tetrahydro-5*H*-tetrazoloazepine.
$C_6H_{10}N_4$=138.2.

CAS — 54-95-5.

Pharmacopoeias. In *Arg., Aust., Belg., Br., Cz., Eur., Fr., Ger., Hung., Ind., Int., It., Jug., Mex., Neth., Nord., Pol., Port., Rus., Span., Swiss,* and *Turk.*

Colourless, almost odourless crystals or white crystalline powder with a slightly pungent bitter taste. M.p. 57° to 60°. **Soluble** 1 in less than 1 of water, of alcohol, and of chloroform, and 1 in less than 4 of ether; soluble in carbon tetrachloride. A 10% solution in water has a pH of 5.5 to 7. A 4.91% solution is iso-osmotic with serum. Solutions are **sterilised** by autoclaving or by filtration, avoiding contact with metal. **Protect** from light.

An aqueous solution of pentetrazol iso-osmotic with serum (4.91%) caused 100% haemolysis of erythrocytes cultured in it for 45 minutes.— E. R. Hammarlund and K. Pedersen-Bjergaard, *J. pharm. Sci.*, 1961, *50*, 24.

Pentetrazol in a concentration of 1 to 3% inhibited the growth of *Escherichia coli, Bacillus subtilis, Staphylococcus aureus,* and *Pseudomonas aeruginosa.* This substantiated the statement in the *B.P.* 1958 that no bactericide needed to be added to solutions for injection.— R. J. Gilbert and A. D. Russell, *Pharm. J.*, 1963, *1*, 111.

Adverse Effects. High dosage produces epileptiform convulsions, and overdosage may result in respiratory depression.

Treatment of Adverse Effects. As for Nikethamide, p.367. If pentetrazol has been ingested the stomach should be emptied by aspiration and lavage.

Precautions. Pentetrazol may provoke seizures in patients with epilepsy or other convulsive disorders.

Absorption and Fate. Pentetrazol is readily absorbed after administration by mouth and by injection. It is rapidly metabolised, chiefly in the liver. About 75% of a parenteral dose has been reported to be excreted in the urine.

Peak plasma concentrations of about 2μg per ml were obtained about 2 hours after a dose of 100 mg of pentetrazol by mouth. The drug was excreted in the urine.— W. R. Ebert *et al.*, *J. pharm. Sci.*, 1970, *59*, 1409.

Plasma-pentetrazol concentrations in 3 patients, who were taking the drug regularly, ranged from 1.45 to 3.1 μg per ml when measured 1.25 to 5 hours after a 100-mg dose.— H. W. Jun *et al.*, *J. pharm. Sci.*, 1975, *64*, 1843.

Uses. Pentetrazol is a respiratory stimulant with actions and uses similar to those of nikethamide (see p.367). It has been given in usual doses of 100 mg, administered subcutaneously, intramuscularly, or intravenously. Pentetrazol has been employed in the elderly to alleviate the symptoms of senility. For this purpose it has been given by mouth in a dose of 100 to 200 mg twice or thrice daily, usually in conjunction with nicotinic acid, but its value has not been substantiated in trials.

Pentetrazol has been administered intravenously as an aid to the diagnosis of epilepsy.

Preparations

Leptazol Injection *(B.P.C. 1963).* Inj. Leptazol. A sterile solution of pentetrazol 10% and sodium phosphate 0.25% in Water for Injections, adjusted to pH 7.8 with dilute hydrochloric acid or potassium hydroxide solution. The addition of a bactericide is unnecessary. *Dose.* 0.5 to 1 ml subcutaneously.

Proprietary Names
Cardiazol *(Knoll, Ger.; Medinsa, Spain; Knoll, Switz.);* Cardiorapide *(Rapide, Spain);* Metrazol *(Knoll, USA).*

1438-g

Phenatine. *N*-(α-Methylphenethyl)nicotinamide diphosphate; *N*-(α-Methylphenethyl)pyridine-3-carboxamide diphosphate.
$C_{15}H_{16}N_2O,2H_3PO_4$=436.3.

CAS — 139-68-4 (base); 2964-23-0 (diphosphate).

Pharmacopoeias. In *Rus.*

Odourless colourless crystals or white crystalline powder with a bitter saline taste. **Soluble** in water and alcohol; practically insoluble in ether. A 5% solution in water has a pH of 1.8 to 2.4.

Uses. Phenatine is claimed to stimulate the central nervous system in a similar way to dexamphetamine without causing vasoconstriction. It is also claimed that it reduces blood pressure. In the USSR it has been employed similarly to dexamphetamine as a central stimulant; it has also been suggested in the treatment of hypertension.

1439-q

Picrotoxin *(B.P. 1963).* Picrotox.; Picrotoxinum; Cocculin.
$C_{30}H_{34}O_{13}$=602.6.

CAS — 124-87-8.

Pharmacopoeias. In *Arg., Int., It., Mex., Span., Swiss,* and *Turk.*

An active principle from the seeds of *Anamirta cocculus* (=*A. paniculata*) (Menispermaceae).
Odourless, colourless, flexible, shining prismatic crystals or white or nearly white microcrystalline powder, with a very bitter taste. M.p. about 199°.
Soluble 1 in 350 of water, 1 in 35 of boiling water, 1 in 16 of alcohol, and 1 in 3 of boiling alcohol; soluble in glacial acetic acid and solutions of acids and alkali hydroxides; slightly soluble in chloroform and ether. A saturated solution in water is neutral to litmus. Solutions are **sterilised** by autoclaving or by filtration. **Protect** from light.

The potency of picrotoxin solutions diminished as the pH increased above 7.— P. W. Ramwell and J. E. Shaw, *J. Pharm. Pharmac.*, 1962, *14*, 321.

Adverse Effects and Treatment. As for Nikethamide, p.367. As little as 20 mg may cause severe poisoning.

Uses. Picrotoxin is a respiratory stimulant with actions and uses similar to those of nikethamide (p.367). Its duration of effect is brief.
It was formerly given in usual doses of 3 to 6 mg intravenously.

1440-d

Pipradrol Hydrochloride *(B.P.C. 1963).* α-(2-Piperidyl)benzhydrol hydrochloride; αα-Diphenyl-α-(2-piperidyl)methanol hydrochloride.
$C_{18}H_{21}NO,HCl$=303.8.

CAS — 467-60-7 (pipradrol); 71-78-3 (hydrochloride).

Odourless, tasteless, small white crystals or white or almost white crystalline powder. M.p. about 290° with decomposition. **Soluble** 1 in 30 of water, 1 in 35 of alcohol, 1 in 1000 of chloroform, and 1 in 8 of methyl alcohol; practically insoluble in ether. A 1% solution in water has a pH of 5 to 7. **Protect** from light.

Adverse Effects. Pipradrol hydrochloride may cause nausea, anorexia, aggravation of anxiety, hyperexcitability, and insomnia. Epigastric discomfort, skin rash, dizziness, and hallucinations have been reported.

Precautions. Pipradrol hydrochloride is contra-indicated in endogenous depression, in agitated prepsychotic patients, chorea, paranoia, obsessional disorders, and anxiety states, and in patients for whom ECT is indicated.

Uses. Pipradrol hydrochloride is a stimulant of the central nervous system which was formerly given in usual doses of 2 to 6 mg daily in fatigue and some depressive states.

Proprietary Names
Detaril *(ISOM, Ital.);* Stimolag Fortis *(Lagap, Switz.).*

1441-n

Cropropamide. *NN*-Dimethyl-2-(*N*-crotonamido)butyramide.
$C_{13}H_{24}N_2O_2$=240.3.

CAS — 633-47-6.

1442-h

Crotethamide. 2-(*N*-Ethylcrotonamido)butyramide.
$C_{12}H_{22}N_2O_2$=226.3.

CAS — 6168-76-9.

1443-m

Prethcamide. G 5668. A mixture of parts by wt of cropropamide and

CAS — 8015-51-8.

Prethcamide is **soluble** in water ether.

Adverse Effects. Side-effects inc paraesthesias, restlessness, muscu tremors, dyspnoea, and flushing. Gastro-intestinal disturbances a have also been reported.

Precautions. Prethcamide should care to patients with epilepsy.

Uses. Prethcamide is a respira which has been given in usual do three or four times daily in the respiratory insufficiency in chronic It has also been given intramusc intravenous injection, and by in sion.

Proprietary Preparations
Micoren *(Geigy, UK).* Prethcamide, a of 400 mg. (Also available as Mico *Neth., Switz.*).

Other Proprietary Names
Micorene *(Belg.).*

1444-b

Prolintane Hydrochloride. S Propylphenethyl)pyrrolidine hydroc
$C_{15}H_{23}N,HCl$=253.8.

CAS — 493-92-5 (prolintane); 12 chloride).

A white odourless powder with M.p. about 133°. **Soluble** in wat chloroform; practically insoluble in

Adverse Effects and Precautions nausea, and tachycardia have been patients receiving prolintane. Th with care in patients taking mono inhibitors, and should not be gi with hyperthyroidism or epilepsy.

Uses. Prolintane hydrochloride is stimulant of the central nervous been given, in fatigue and to in usually with vitamin supplements 10 mg twice daily, with the secon given not later than mid-afternoon.

Proprietary Preparations
Villescon *(Boehringer Ingelheim, UK)* in each 5 ml prolintane hydrochloride hydrochloride 1.67 mg, riboflavine phos salt) 1.36 mg, pyridoxine hydrochloride namide 5 mg, and alcohol 12.2% w/v (in water) and **Tablets** each containing pr chloride 10 mg, thiamine mono-nitrate 5 3 mg, pyridoxine hydrochloride 1.5 mg 15 mg, and ascorbic acid 50 mg. For th of appetite and mood. *Dose.* 10 ml of li twice daily; children 5 to 12 years, 2.5 to

Other Proprietary Names
Promotil *(Fr.).*

National Library of Medicine: IGM Full Record Screen

Diagnostic aid of epilepsy

TITLE:	**Facilitation of pentylene tetrazole-kindled seizures by mild thyroid hormone deficiencies.**
AUTHOR:	**Pacheco-Rosado J; Angeles-Lopez L**
AUTHOR AFFILIATION:	**Department of Physiology Mauricio Russek, Escuela Nacional de Ciencias Biologicas, I.P.N., Mexico, D.F.**
SOURCE:	**Proc West Pharmacol Soc 1997;40:75-7**
NLM CIT. ID:	**98098613**
MAIN MESH SUBJECTS:	**Convulsants/*TOXICITY Kindling (Neurology)/*PHYSIOLOGY Pentylenetetrazole/*TOXICITY Triiodothyronine/BLOOD/*DEFICIENCY**
ADDITIONAL MESH SUBJECTS:	**Animal Dose-Response Relationship, Drug Hypothyroidism/BLOOD Male Rats Rats, Wistar Support, Non-U.S. Gov't Time Factors**
PUBLICATION TYPES:	**JOURNAL ARTICLE**
LANGUAGE:	**Eng**
REGISTRY NUMBERS:	**0 (Convulsants) 54-95-5 (Pentylenetetrazole) 6893-02-3 (Triiodothyronine)**

Order Documents | 92 67 71 Other Years | Log off IGM
Next Record | Details Of Search | Return to Results | Return to Search Screen | Previous Record

National Library of Medicine: IGM Full Record Screen

TITLE: Synthesis, anticonvulsant and analgesic activities of some 6-substituted imidazo(2,1-b)-1,3,4-thiadiazole-2-sulfonamides and their 5-bromo derivatives.

AUTHOR: Khazi IA; Mahajanshetti CS; Gadad AK; Tarnalli AD; Sultanpur CM

AUTHOR AFFILIATION: Department of Chemistry, Karnatak University, Dharwad (India).

SOURCE: Arzneimittelforschung 1996 Oct;46(10):949-52

NLM CIT. ID: 97085798

ABSTRACT: A series of 6-substituted imidazo(2,1-b)-1,3,4-thiadiazole-2-sulfonamides (V) were prepared by condensation of 2-amino-1,3,4-thiadiazole-5-sulfonamide (II) with an appropriate 2-bromo-ketone (III). Bromination of V in glacial acetic acid gave the corresponding 5-bromo derivatives (VI). Five selected compounds (15-18 and 28) were evaluated for their anticonvulsant and analgesic activities. Compounds 15-17 showed maximum protection (83%) against pentylene tetrazole induced convulsions and maximum electroshock induced seizures while the standard phenobarbital sodium and phenytoin sodium showed 100% protection, respectively. Compounds 15, 16 and 18 showed superior analgesic activity to acetylsalicylic acid in rat caudal immersion test.

Diagnostic use

MAIN MESH SUBJECTS: Analgesics/*CHEMICAL SYNTHESIS/PHARMACOLOGY/TOXICITY
Anticonvulsants/*CHEMICAL SYNTHESIS/PHARMACOLOGY/TOXICITY
Sulfonamides/*CHEMICAL SYNTHESIS/PHARMACOLOGY

ADDITIONAL MESH SUBJECTS:	**Animal** **Convulsants** **Dose-Response Relationship, Drug** **Electroshock** **Female** **Indicators and Reagents** **Male** **Mice** **Pain Measurement/DRUG EFFECTS** **Pentylenetetrazole/ANTAGONISTS & INHIB** **Rats** **Rats, Wistar** **Spectrophotometry, Infrared**
PUBLICATION TYPES:	**JOURNAL ARTICLE**
LANGUAGE:	**Eng**
REGISTRY NUMBERS:	**0 (Analgesics)** **0 (Anticonvulsants)** **0 (Convulsants)** **0 (Indicators and Reagents)** **0 (Sulfonamides)** **54-95-5 (Pentylenetetrazole)**

Order Documents | 92, 67-71 Other Years | Log off IGM
Next Record | Details Of Search | Return to Results | Return to Search Screen | Previous Record

TITLE:	Synthesis and biological activities of some 3,6-disubstituted thiazolo[3,2-b][1,2,4]triazoles.
AUTHOR:	Erol DD; Calis U; Demirdamar R; Yulug N; Ertan M
AUTHOR AFFILIATION:	Hacettepe University, Faculty of Pharmacy, Pharmaceutical Chemistry Department, Ankara, Turkey.
SOURCE:	J Pharm Sci 1995 Apr;84(4):462-5
NLM CIT. ID:	95356086
ABSTRACT:	Some new 2,3-dihydro-3-hydroxy-6-phenyl-3-(4-substituted-(phenylthiazolo[3,2-b][1,2,4]triazole derivatives were synthesized as antifungal agents. After their structures were confirmed by microanalysis and IR and NMR spectral analysis, their antifungal activities against Candida albicans, Candida parapsilosis, Candida stellatoidea, and Candida pseudotropicalis were investigated. Contrary to our expectations, all proved to have poor antifungal activities. Because 2,4-dihydro-3H-1,2,4-triazol-3-ones are a new class of anticonvulsant agents, a series of thiazolo[3,2-b][1,2,4]triazoles was evaluated for anticonvulsant activity and observed as potential anticonvulsant candidates. All compounds examined exhibited activity against both maximal electroshock and pentylene tetrazole-induced seizures in mice.
MAIN MESH SUBJECTS:	Anticonvulsants/*CHEMICAL SYNTHESIS/PHARMACOLOGY Antifungal Agents/*CHEMICAL SYNTHESIS/PHARMACOLOGY Thiazoles/*CHEMICAL SYNTHESIS/PHARMACOLOGY Triazoles/*CHEMICAL SYNTHESIS/PHARMACOLOGY
ADDITIONAL MESH SUBJECTS:	Animal Candida/DRUG EFFECTS Convulsions/CHEMICALLY INDUCED/PREVENTION & CONTROL Electroshock Male Mice Microbial Sensitivity Tests Pentylenetetrazole Spectrophotometry, Infrared
PUBLICATION TYPES:	JOURNAL ARTICLE
LANGUAGE:	Eng
REGISTRY NUMBERS:	0 (Anticonvulsants) 0 (Antifungal Agents) 0 (Thiazoles) 0 (Triazoles) 54-95-5 (Pentylenetetrazole)

A. INGREDIENT NAME:

PIRACETAM

B. Chemical Name:

1-Acetamido-2-Pyrrolidinone, Euvicor, Gabacet, Genogris, 2-Ketopyrrolidine-1-Ylacetamide, Nootron, Nootropil, Nootropyl, Normabrain, 2-Oxo-Pyrrolidine-Acetamide, 2-Oxo-Pyrrolidin-1-Ylacetamide, Piracetam, Pirazetam, Pirroxil, Pyracetam, Pyramem, 2-Pyrrolidininnoneacetamide, 2-Pyrrolidoneacetamide, UCB 6215

C. Common Name:

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

Assay: 99.27%

E. Information about how the ingredient is supplied:

White or almost white crystal powder

F. Information about recognition of the substance in foreign pharmacopeias:

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Mondadori, C. Nootropics: Preclinical Results in the Light of Clinical Effects; Comparison with Tacrine. *Critical Reviews™ in Neurobiology*, 1996; 10: 357-370.

Tallal, U., Chase, C., and Russell, G. Calculation of the Efficacy of Piracetam in Treating Information Processing, Reading, and Writing Disorders in Dyslexic Children. *International Journal pf Psychophysiology*, 1986; 4: 41-52.

Mindus, P., Cronholm, B., and Levander, S. E. Piracetam-induced improvement of mental performance: a controlled study on normally aging individuals. *Acta Psychiat. Scand.*, 1976; 54(2):150-160.

Simeon, J., Waters, B., and Resnick, M. Effects of Piracetam in children with learning disorders. *Psychopharmacol.Bull.*, 1980; 16: 65-66.

Stegink, K. J., The clinical use of Piracetem, a new nootropic drug: the treatment of senile involution. *Arzneim-Forsch,* 1972; 22: 975-977.

Wilsher, C., Atkins, G., and Mansfield, P. Piracetam as an aid to learning in dyslexia, preliminary report. *Psychopharmacology.* 1979; 65: 107-109.

Wilsher, C., Atkins, G., and Mansfield, P. Effects of Piracetam on dyslexic' reading ability. *J. Learn. Disability.* 1985; 18: 19-25.

Mondadori, C., Petschke, F., and Häusler, A. The Effects of Nootropics on Memory: new Aspects for Basic Research. *Pharmacopsychiatry.* 1989; 22: 102-106.

YaI, V., Derzhiruk, L. P., and Mogilevskii, A. Piracetam-induced changes in the functional activity of neurons as a possible mechanism for the effects of nootropic agents. *Neurosci Behav. Physiol.*, 1996; 26(6): 507-515.

Pepeu, G. and Spignoli, G. Nootropic drugs and brain cholinergic mechanisms. *Prog. Neuropsychopharmacol Biol. Psychiatry.* 1989; 13Suppl: S77-78.

Pilch, H. and Muller, W. E. Piracetam elevates muscarinic cholinergic receptor density in the frontal cortex of aged but not of young mice. *Psychopharmacology.* 1988; 94(1): 74-78.

De Deyn, P. P., Reuck, J. D., and Deberdt, W. Treatment of acute ischemic stroke with Piracetam. Members of the Piracetam in Acute Stroke Study (PASS) Group. *Stroke.* 1997; 28(12): 2347-2352.

Di Ianni, M., Wilsher, C. R., and Blank, M. S. The effects of Piracetam in children with dyslexia. *J. Clin Psychopharmacol.* 1985; 5(5): 272-278.

Wilsher, C. R., Bennett, D., and Chase, C. H. Piracetam and dyslexia: effects on reading tests. *J. Clin Psychopharmacol.* 1987; 7(4): 230-237.

Reisberg, B., Ferris, S. H., and Gershon, S. An overview of pharmacologic treatment of cognitive decline in the aged. *Am J. Psychiatry.* 1981; 138(5): 593-600.

Bartus, R. T., Dean, R. L., and Sherman, K. A. Profound effects of combining choline and Piracetam on memory enhancement and cholinergic function in aged rats. *Neurobiol Aging.* 1981; 2(2): 105-111.

Buresova, O. and Bures, J. Piracetam-induced facilitation of interhemispheric transfer of visual information in rats. *Psychopharmacologia.* 1976; 46(1): 93-102.

Dimond, S. J., Scammell, R. E., and Pryce, I. G. Some effects of Piracetam (UCB 6215, Nootropyl) on chronic schizophrenia. *Psychopharmacology.* 1979; 64(3): 341-348.

Dimond, S. J. and Brouwers, E. M. Increase in the power of human memory in normal man through the use of drugs. *Psychopharmacology.* 1976; 49(3): 307-309.

Sara, S. J., David-Remacle, M., and Weyers, M. Piracetam facilities retrieval but does not impair extinction of bar-pressing in rats. *Psychopharmacology.* 1979; 61(1): 71-75.

Brandao, F., Paula-Barbosa, M. M., and Cadete-Leite, A. Piracetam impedes neuronal loss withdrawal after chronic alcohol intake. *Alcohol.* 1995; 12(3): 279-288.

Mindus, P., Cronholm, B., and Levander, S. E. Does Piracetam counteract the ECT-induced memory dysfunctions in depressed patients? *Acta Psychiatr. Scand.* 1975; 52(5): 319-326.

Mondadoori, C., Classen. W., and Borkowski, J. Effects of oxiracetam on learning memory in animals: comparison with piracetam. *Clin Neuropharmacol.* 1986; 9 Suppl 3 S27-38.

Song, C., Earley, B., and Leonard, B. E. Effect of chronic treatment with piracetam and tacrine on some changes caused by thymectomy in the rat brain. *Pharmacol Biochem. Behav.* 1997; 56(4): 697-704.

H. Information about dosage forms used:

Patients received either 3.3 g of Piracetam daily or matching placebo syrup. Each dose of test medication was 5 ml. administered before breakfast and again before the evening meal. A 5 ml dose of active medication contained 1.65 g of Piracetam. No dosage adjustments were allowed. The patient's parents were contacted to review dosage instructions and to determine whether any adverse effects had been observed.

I. Information about strength:

1.65 g -3.3 g

J. Information about route of administration:

Orally

K. Stability data:

L. Formulations:

M. Miscellaneous Information:

See File

CERTIFICATE OF ANALYSIS

30-3213
54051

Coa No: 7777

PIRACETAM

Batch No: 96120006

Manufacturing Date: Dec 3, 1996

Testing Result

Appearance	White or almost white crystal powder
Identification	Positive
Melting Point	152.5-153.5°C
Clarity of Solution	Clear
Heavy Metals	<20ppm
Residue on Ignition	0.02%
Loss on Drying	0.12%
Assay	99.27%

Conclusion: Conforms to China Provincial Standard

Remarks: The above testing result is per manufacturer's information.

10/97

QUALITY CONTROL REPORT

CHEMICAL NAME.: PIRACETAM

MANUFACTURE LOT NO.: 97060036

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP__/BP__/MERCK__/NF__/MART.__/CO.SPECS.___.

1) DESCRIPTION.:
WHITE TO OFF WHITE CRYSTALS FROM ISOPROPANOL OR WHITE TO OFF WHITE CRYSTALLINE POWDER.

2) SOLUBILITY.:
VERY SOLUBLE IN WATER; SOLUBLE IN ALCOHOL, ESPECIALLY IN ISOPROPANOL.

3) MELTING POINT.:
MELTS AT ABOUT 151.5-152.5 degree.

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:
A) COMPLIES IR SPECTRUM AS PER COMPANY SPECS.

PASSES.:_____ **FAILS.:**_____

COMMENTS.:

ANALYST SIGNATURE.:_____ **DATE.:**_____

PREPACK TEST.:_____ **DATE.:**_____ **INITIAL.:**_____

RETEST.:_____ **DATE.:**_____ **INITIAL.:**_____

---------- IDENTIFICATION ----------

PRODUCT #: P5295 NAME: PIRACETAM

CAS #: 7491-74-9

MF: C6H10N2O2

SYNONYMS

1-ACETAMIDO-2-PYRROLIDINONE * EUVIFOR * GABACET * GENOGRIS * 2-KETOPYRROLIDINE-1-YLACETAMIDE * NOOTRON * NOOTROPIL * NOOTROPYL *

NORMABRAIN * 2-OXO-PYRROLIDINE ACETAMIDE * 2-OXO-PYRROLIDIN-1-

YLACETAMIDE * PIRACETAM * PIRAZETAM * PIRROXIL * PYRACETAM * PYRAMEM *

2-PYRROLIDINONEACETAMIDE * 2-PYRROLIDONEACETAMIDE * UCB 6215 *

---------- TOXICITY HAZARDS ----------

RTECS NO: UX9660500

1-PYRROLIDINEACETAMIDE, 2-OXO-

TOXICITY DATA

IPR-MUS LD50:>10 GM/KG	PCJOAU 23,795,89
SCU-MUS LD50:12 GM/KG	KHFZAN 11(8),132,77
IVN-MUS LD50:10 GM/KG	KHFZAN 11(8),132,77
IVN-CAT LD50:10 GM/KG	RPTOAN 47,205,84
UNR-MAM LD50:>10 GM/KG	RPTOAN 44,22,81

ONLY SELECTED REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES (RTECS)

DATA IS PRESENTED HERE. SEE ACTUAL ENTRY IN RTECS FOR COMPLETE INFORMATION.

---------- HEALTH HAZARD DATA ----------

ACUTE EFFECTS

MAY BE HARMFUL BY INHALATION, INGESTION, OR SKIN ABSORPTION.

MAY CAUSE IRRITATION.

EXPOSURE CAN CAUSE:

CNS STIMULATION

THE TOXICOLOGICAL PROPERTIES HAVE NOT BEEN THOROUGHLY INVESTIGATED.

FIRST AID

IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS CONSCIOUS.

CALL A PHYSICIAN.

IN CASE OF SKIN CONTACT, FLUSH WITH COPIOUS AMOUNTS OF WATER

FOR AT LEAST 15 MINUTES. REMOVE CONTAMINATED CLOTHING AND

SHOES. CALL A PHYSICIAN.

IF INHALED, REMOVE TO FRESH AIR. IF BREATHING BECOMES DIFFICULT,

CALL A PHYSICIAN.
IN CASE OF CONTACT WITH EYES, FLUSH WITH COPIOUS AMOUNTS OF WATER

FOR AT LEAST 15 MINUTES. ASSURE ADEQUATE FLUSHING BY SEPARATING

THE EYELIDS WITH FINGERS. CALL A PHYSICIAN.

---------- PHYSICAL DATA ----------

APPEARANCE AND ODOR

SOLID

---------- FIRE AND EXPLOSION HAZARD DATA ----------

EXTINGUISHING MEDIA

WATER SPRAY.

CARBON DIOXIDE, DRY CHEMICAL POWDER OR APPROPRIATE FOAM.

SPECIAL FIREFIGHTING PROCEDURES

WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING TO

PREVENT CONTACT WITH SKIN AND EYES.

UNUSUAL FIRE AND EXPLOSIONS HAZARDS

EMITS TOXIC FUMES UNDER FIRE CONDITIONS.

---------- REACTIVITY DATA ----------

STABILITY

STABLE.

HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS

THERMAL DECOMPOSITION MAY PRODUCE CARBON MONOXIDE, CARBON DIOXIDE,

AND NITROGEN OXIDES.

HAZARDOUS POLYMERIZATION

WILL NOT OCCUR.

---------- SPILL OR LEAK PROCEDURES ----------

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

WEAR PROTECTIVE EQUIPMENT.

SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL.

AVOID RAISING DUST.

VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS COMPLETE.

WASTE DISPOSAL METHOD

DISSOLVE OR MIX THE MATERIAL WITH A COMBUSTIBLE SOLVENT AND BURN IN A

CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER.

OBSERVE ALL FEDERAL, STATE, AND LOCAL LAWS.

--- PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE ---

WEAR APPROPRIATE NIOSH/MSHA-APPROVED RESPIRATOR, CHEMICAL-RESISTANT

GLOVES, SAFETY GOGGLES, OTHER PROTECTIVE CLOTHING.

MECHANICAL EXHAUST REQUIRED.
CAUTION:
AVOID CONTACT AND INHALATION.

THE ABOVE INFORMATION IS BELIEVED TO BE CORRECT BUT DOES NOT PURPORT TO BE
ALL INCLUSIVE AND SHALL BE USED ONLY AS A GUIDE. SIGMA ALDRICH SHALL NOT BE
HELD LIABLE FOR ANY DAMAGE RESULTING FROM HANDLING OR FROM CONTACT WITH THE
ABOVE PRODUCT. SEE REVERSE SIDE OF INVOICE OR PACKING SLIP FOR ADDITIONAL
TERMS AND CONDITIONS OF SALE

patients with Alzheimer's disease. *Arch Neurol* (United States) 49(11): 1137-41, November 1992.

Scrofani A, Biondi R, Sofia V, D'Alpa F, Grasso A and Filetti S. EEG patterns of patients with cerebrovascular damage. Effect of L-acetylcarnitine during sleep *Clin Trials J* (United Kingdom) 25(Suppl. 1): 65-71, 1988.

Sershen H, Harsing LG Jr, Banay-Schwartz M, Hashim A, Ramacci MT and Lajtha A. Effect of acetyl-L-carnitine on the dopaminergic system in aging brain. *J Neurosci Res* (USA) 30(3): 555-59, 1991.

Sinforiani E, Iannuccelli M, Mauri M, Costa A, Merlo P, Bono G and Nappi G. Neuropsychological changes in demented patients treated with acetyl-L-carnitine. *Int J Clin Pharmacol Res* 10(1-2): 69-74, 1990.

Tempesta E, Casella L, Pirrongelli C, Janiri L, Calvani M, Ancona L. L-acetylcarnitine in depressed elderly subjects. A cross-over study vs. placebo. *Drugs Under Experimental Clinical Research* 13(7): 417-23, 1987.

Tempesta E, Troncon R, Janiri L, Colusso L, Riscica P, Saraceni G, Gesmundo E, Calvani M, Benedetti N and Pola P. Role of acetyl-L-carnitine in the treatment of cognitive deficit in chronic alcoholism. *Int J Clin Pharmacol Res* 10(1-2): 101-7, 1990.

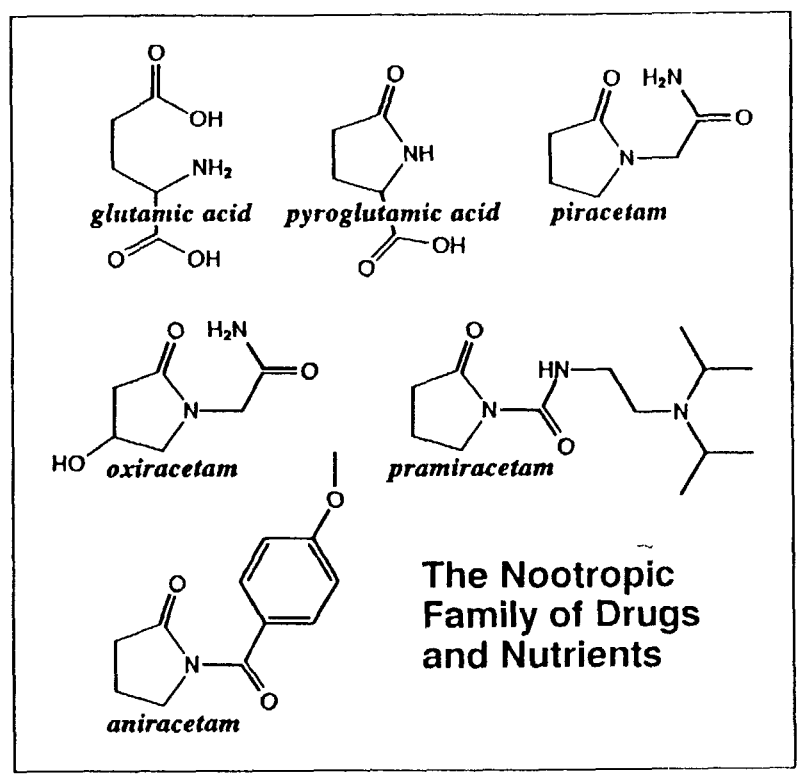
Vecchi GP, Chiari G, Cipolli C, Cortelloni C, De Vreese L and Neri M. Acetyl-L-carnitine treatment of mental impairment in the elderly: Evidence from a multicentre study. *Arch Gerontol Geriatr* (Netherlands) 12(Suppl. 2): 159-68, 1991.

Villardita C, Smirni P and Vecchio I. N-acetylcarnitine in depressed elderly patients [L'Acetil carnitina nei disturbi della sfera affettiva dell'anziano]. *Eur Rev Med Pharmacol Sci* (Italy) 6(2): 341-44, 1984.

Piracetam Update

This unique substance is probably the most popular smart drug for normal, healthy people. We've received many positive comments about piracetam in the smart-drug fan mail. Some of the most interesting of these piracetam stories (and a couple of mild caveats) are included in the Smart Drug Users chapter of this book.

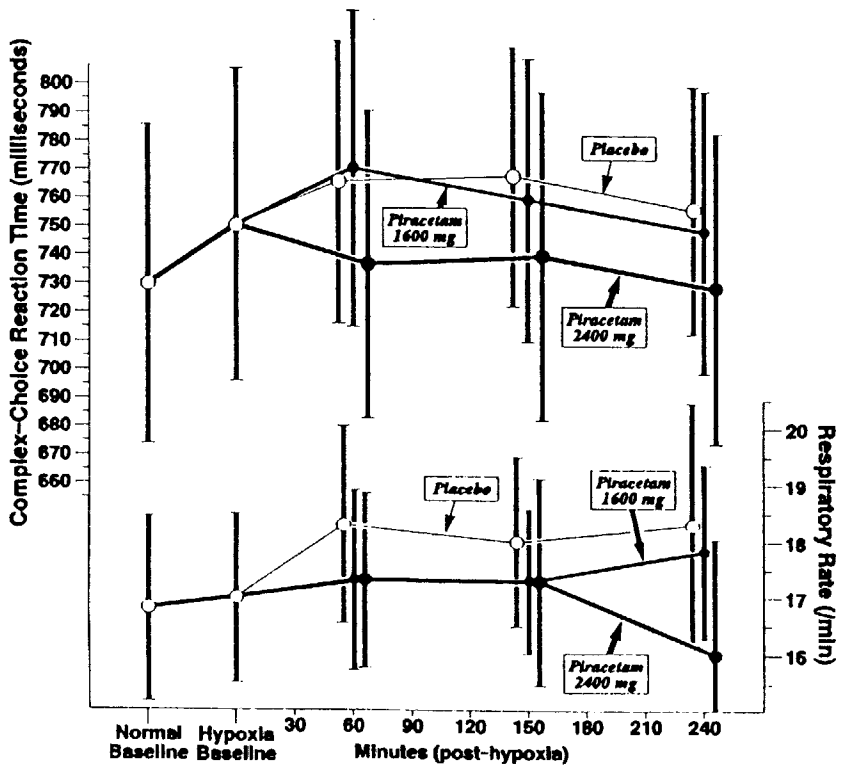
In the three years since *Smart Drugs & Nutrients* was researched and published, over 150 papers have appeared in the world's scientific literature which describe human studies of piracetam. Piracetam is, in fact, a broadly effective enhancer of many



aspects of human performance. The studies presented in this chapter clearly indicate the breadth of piracetam's clinical application. These studies amply illustrate piracetam's benefits for normal, healthy adults, normally aging elderly adults, and people suffering from overt cognitive disorders like senility and Alzheimer's disease.

Piracetam and Weekend Athletes

The ability of piracetam to reduce metabolic stress under low-oxygen conditions was investigated by Schaffler and Klausnitzer in 1988. The researchers induced hypoxia (low oxygen levels) in healthy young men (early 20s to early 30s) by reducing the oxygen content of the laboratory air that they breathed by about half (10.5% instead of 20% oxygen). This resembled "the



oxygen supply at an altitude of about 5300 meters" (17,400 feet). The degree of cognitive impairment due to the low oxygen levels was investigated, and the ability of piracetam (in single doses of 1600 mg or 2400 mg) to prevent this impairment was measured (see opposite figure). Half of the group was given a placebo.

Various tests of reaction time were performed, and in all cases, the piracetam-treated group performed better. Best results were obtained at the higher dose (see opposite figure, upper data points). The increased breathing rate that is usually seen under low oxygen conditions was significantly reduced by a single dose of piracetam (lower data points).

The significance of these results is that normal, healthy people who travel from lower altitudes to higher altitudes for physical activities that require stamina, coordination, concentration, and muscular output are likely to greatly benefit from piracetam. Skiers, take note! Smart-drugged skiers on vacation are probably less likely to injure themselves or someone else, and may be more likely to enjoy their vacation. Piracetam will probably not only make high-altitude sports safer, but is likely to improve performance as well.

Other high-altitude activities likely to be safer with piracetam include mountain bicycling, backpacking, rock climbing, hang gliding, and bungee jumping. And piracetam is likely to improve performance of the sport.

All of these activities involve some risk. Statistically speaking, compared to taking piracetam these sports are absolutely throw-caution-to-the-wind dare-devilish. Recently a bungee jumping trainer forgot to attach his own bungee to the mooring and jumped to his death. Would he have forgotten if he had taken piracetam? The research points to a decrease in the odds of making just this kind of error.

Piracetam for Cigarette Smokers

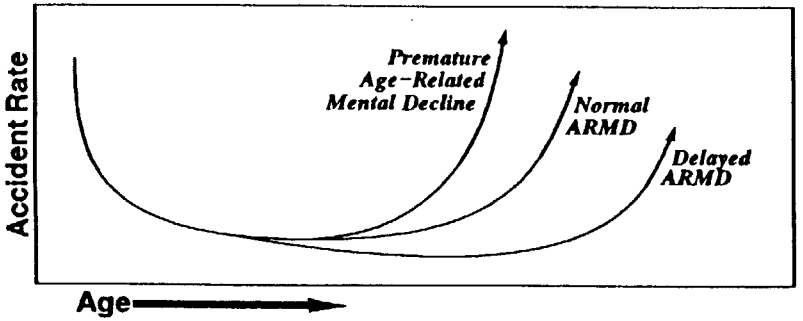
Of even more potential significance is the possibility that other disease conditions resulting from low oxygen levels in the blood

may also be alleviated by piracetam. For example, a two-pack-per-day cigarette smoker at sea level has the oxygen levels of a person at 10,000 feet. Also, many clinical conditions like atherosclerosis (occluded arteries) and many pulmonary diseases (especially emphysema) cause reduced blood and brain oxygenation. Piracetam may greatly relieve the adverse effects of oxygen shortage in these conditions.

Driving Skills in Elderly Motorists

Statistically, middle-aged drivers have the lowest accident rates. The rate of age-related accidents can be represented by a graph with a U-shaped curve (see illustration below) with the highest values in the late teens (learning to drive) and early twenties (learning traffic judgment), the lowest values in middle age (maximum skill, experience and judgment), and higher levels again at advanced ages (impaired vision, hearing, reaction time and/or judgment).

One study of elderly drivers (average age 62.7 years) showed slightly diminished performance in "driving tasks" as compared to middle-aged drivers (average age 40.6 years). This decrement was characterized by significantly diminished performance in sign observance, lane discipline, hesitant driving, technical handling, and "junction alertness" (leading to "twice as many risk situations which required driving-instructor intervention"). No differences in speed or safe-distance behavior were noted between the groups.



Could piracetam alter the shape of the accident curve and alleviate these decrements in older drivers by delaying the onset and slowing the progression of age-related changes?

A recent study conducted at the University of Cologne in Germany was performed to answer this question [Schmidt, 1991]. The researchers examined the driving skills of 101 elderly drivers with "reduced reaction capacity." In a randomized, double-blind, placebo-controlled study, in real-traffic conditions, those patients treated with piracetam exhibited significantly improved performance. Over the six-week test period, piracetam-treated drivers' "sign-observance" scores improved from 77.08% pre-treatment to 84.16% post-treatment.

This study indicates clearly that some of the age-related reductions in driving performance can be improved by piracetam. In only six weeks, the piracetam-treated drivers improved 7.08% on the sign-observance test. Of particular interest is the authors' note that "*all* of the drivers who scored less than 80% improved when treated with piracetam." This indicates that piracetam is most helpful in those people with the greatest driving impairment.

The number and percentage of elderly drivers in developed countries is increasing, as birth rates drop and life-expectancy increases. The extent to which widespread piracetam use by elderly drivers might diminish the rising costs of accidents caused by elderly drivers is not yet known, but it is certainly worth investigating.

Changes in Attitudes

Only three years ago, smart-drug critics were focusing on the lack of human testing in normal, healthy individuals. They said, "just because piracetam corrects cognitive deficits caused by disease doesn't mean it will correct cognitive deficits caused by aging, or that it will enhance cognitive abilities in healthy

people." However, increasing data now confirm that piracetam does, in fact, improve cognitive performance in normal people.

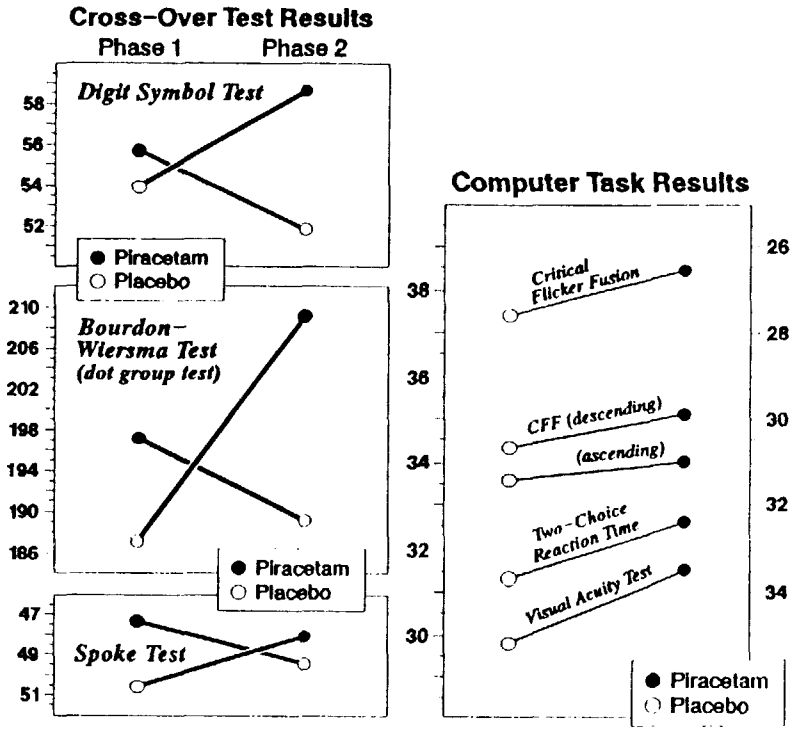
One of the first pioneering studies to investigate this possibility was conducted 17 years ago in Sweden long before the complaints of smart-drug critics [Mindus, 1976]. These researchers selected late-middle-aged test subjects (50 years and older) of above average intelligence (their IQs averaged above 120) and who were otherwise healthy (none had any clinical signs of rapidly deteriorating mental abilities).

All 18 test subjects reported "slight but seemingly permanent reduction for some years in their capacity to retain or recall information" (AAMI). They all had developed compensatory strategies and behaviors to continue in their highly demanding jobs, such as "taking notes" and "working slower." All in all, these subjects were a good cross-section of the more productive and accomplished senior members of the work force.

The researchers employed a double-blind, cross-over study. Half of the test subjects were given placebo for the first four weeks (phase 1), and piracetam (4.8 grams daily) for the second four weeks (phase 2). The other half were given piracetam first, and placebo second.

The subjects then took a number of performance tests, including computer-based tests. In all phases of testing, piracetam scores were higher. In the cross-over phase, all subjects who switched from placebo to piracetam improved in score, and all subjects who switched from piracetam to placebo lowered in score (see the graphs below).

The computer-test results were converted into like-magnitude units to illustrate the similarity of the performance increases from piracetam. It can be seen that all five computerized tests showed identical magnitude gains. This is certainly a striking observation, given the selective effects of some other smart drugs. Piracetam and other nootropic drugs seem to produce positive effects in many aspects of mental function.



Claims that smart drugs have not proven effective on normal, healthy people are clearly wrong. Such allegations are not based on science, but rather on the personal prejudices of the accusers and their unfamiliarity with the scientific literature.

Cognitive Enhancement in Senility

Although some critics may criticize the use of smart drugs to treat AAMI, many acknowledge that smart drugs *are* effective in the treatment of overt senile cognitive impairment. In a recent study of 84 geriatric patients with non-vascular senile cognitive deterioration, piracetam was found to be better than a placebo at enhancing several cognitive abilities, including attention, memory, and behavior [Fioravanti, 1991]. Dosages of 6 grams per day appeared to be more effective than 3 grams

per day. However, once optimum benefits had been obtained on the 6-gram-per-day dose, the 3-gram-per-day dose was adequate to maintain the cognitive gains induced by the higher dose.

Cognitive Performance in Epileptics

Anti-epileptic medicines often exhibit cognitive side effects in the inverted-U dose-response manner. For example, at low doses, many anti-epileptic drugs improve cognition scores. However, at the high doses often necessary to control epileptic seizures, anti-epileptic drugs can cause profound cognitive impairment.

In a new study of the cognitive properties of piracetam in epileptic patients, piracetam was found to significantly improve cognitive test results without interfering with the efficacy of anti-epileptic medications. Patients taking one anti-seizure drug (carbamazepine) appeared to have even greater seizure protection when the carbamazepine was combined with piracetam [Chaudhry, 1992].

New Research Trends

Recent research into the mechanisms of nootropic drugs (drugs in the same class as piracetam) is shedding light on the crucial question, "How does piracetam work?" New findings point to a number of modes of action, including 1) stimulation of glucose metabolism, 2) increased ATP turnover, 3) increased 'internal messenger' (cyclic AMP, or cAMP) levels, 4) enhanced phospholipid levels, 5) increased protein biosynthesis, and 6) increased cholinergic and dopaminergic stimulation. Nootropics also seem to produce resistance to several neurotoxic substances, and stimulate learning through influences on the hippocampus and cortex. Oxygen utilization by the brain appears to be significantly enhanced. [Schaffler, *et al.*, 1988].

The Recognition Piracetam Deserves

It is long past time to recognize and acknowledge that piracetam does indeed enhance cognition in both normal healthy people *and* the cognitively impaired. In 1990, piracetam sales from one brand alone (Nootropil, UCB) topped *one billion dollars* worldwide. According to UCB's annual report, Nootropil sales are still increasing, years after their patent on piracetam has expired, and numerous competitive generic piracetam products have entered the market. After decades of completely safe use, and millions of prescription and over-the-counter sales in many countries, we believe that it's time for the United States to join the rest of the world in approving piracetam for its citizens. Piracetam's absence of any known toxicity makes it an ideal candidate for over-the-counter status.

Precautions

Piracetam may increase the effects of certain drugs, such as amphetamines, psychotropics, and Hydergine, as previously stated. Adverse effects are extremely rare, but include insomnia, psychomotor agitation, nausea, gastrointestinal distress, and headaches. Piracetam has no known toxicity or contraindications.

Dosage

Piracetam is supplied in 400 mg or 800 mg capsules or tablets. The usual dose is 2400 to 4800 mg per day in three divided doses. Some literature recommends a high "attack" dose be taken for the first two days. We have noticed that often when people first take piracetam they do not notice any effect at all until they take a high dose (approximately 4000 to 8000 mg). Thereafter, they may notice that a lower dosage is sufficient. Piracetam takes effect within 30 to 60 minutes.

Note that piracetam seems to synergize with other smart drugs. If piracetam is combined with other smart drugs, the dosage of one or more drugs/nutrients may need to be reduced.

Sources

Piracetam is not available in the U.S. but can be easily ordered from most overseas mail-order pharmacies. An up-to-date listing of such overseas sources is maintained by CERI (see the tearout card at the front of this book).

References

Chaudhry HR, Najam N, De Mahieu C, Raza A, Ahmad N. Clinical use of piracetam in epileptic patients. *Curr Ther Res Clin Exp* 52(3): 355-60, 1992.

Fioravanti M, Bergamasco B, Bocola V, *et al.*. A multicentre, double-blind, controlled study of piracetam vs. placebo in geriatric patients with nonvascular mild-moderate impairment in cognition. *New Trends in Clinical Neuropharmacology* (Italy) 5(1): 27-34, 1991.

Mindus P, Cronholm B, Levander SE, and Schalling D. Piracetam-induced study on normally aging individuals. *Acta Psychiat Scand* 54: 150-60, 1976.

Schaffler K and Klausnitzer W. Randomized placebo-controlled double-blind cross-over study on antihypoxidotic effects of piracetam using psychophysiological measures in healthy volunteers. *Arzneim-Forsch* 38(2): 288-91, 1988.

Schmidt U, Brendemuhl D, Engels K, *et al.*. Arbeits und Forschungsgemeinschaft fur Strassenverkehr und Verkehrssicherheit. *Pharmacopsychiatry* (Germany) 24(4): 121-26, July 1991.

Vitamin Update

When *Smart Drugs & Nutrients* was written in 1990, vitamins were still considered "fringe science" by many in the medical profession. Nevertheless, we reviewed in that book some of the scientific evidence on the cognitive-performance-enhancing benefits of vitamins.

Since the publication of *Smart Drugs & Nutrients*, there seems to have been a paradigm shift away from the bad old days of physicians warning against vitamins, to a new consensus in the scientific and medical community that vitamins are potent disease fighters and potential aging-retardants.

On April 6, 1992, *Time* magazine published a cover story on vitamins, proclaiming that, "New evidence shows they may help fight cancer, heart disease, and the ravages of aging." A mere ten years ago, such a story would have generated a storm of protest from medical authorities. Today, the ever-mounting evidence for the abilities of nutrients to prevent and treat disease is so overwhelming that only a few die-hard anti-vitamin medical "authorities" remain vocal critics. Vitamins are now mainstream.

As Barbara Walters commented on ABC's *Nightline*, "There was a time when doctors said, 'Eat a balanced diet and you don't have to take vitamins.' Now we are learning that this vitamin or that vitamin might help prevent cancer." At the 1992 *American Aging Association* Conference in San Francisco, one researcher volunteered that nearly everyone in the field of gerontology (the study of aging) is now taking megadoses of vitamins. Ten years ago, only a few were.

Approximately half of all Americans take vitamin supplements and about half of those take daily supplements. Americans spend $3.3 billion on vitamins and nutrients every year — and that figure is growing.

Critical Reviews™ in Neurobiology, 10(3&4):357–370 (1996)

Nootropics: Preclinical Results in the Light of Clinical Effects; Comparison with Tacrine

Cesare Mondadori

Hoechst Marion Roussel, CNS Research, P. O. Box 6800, Bridgewater, NJ 08807–0800

ABSTRACT: This review is meant to serve several purposes. First, it surveys the preclinical and clinical profiles of piracetam-like nootropics. Second, the conditions under which the nootropics are active in preclinical studies are identified and analyzed with a view to finding a common denominator that could explain the observed effects. Third, the clinical profile is examined, on the one hand to assess whether these drugs are in fact active in humans, and on the other to determine how the clinical effects of the nootropics compare with those of tacrine. Lastly, the clinical data are then further scrutinized to assess whether they fulfill the expectations based on the preclinical findings.

KEY WORDS: Nootropics, piracetam, oxiracetam, pramiracetam, aniracetam, tacrine, preclinical, clinical, responders, nonresponders.

INTRODUCTION

The discovery of piracetam[1] shook faith in Paracelsus' famous axiom, "dosis facit venenum." This memory improving substance not only was devoid of other biological activity but also had no toxic effects whatever at doses up to grams per kilogram of body weight. Even today, nearly 30 years after the discovery, the "nootropic" class of substances[2] newly created to accommodate piracetam still splits pharmacologists into two camps. For some, the absence of toxicity indicates a lack of any pharmacological action, while others see it as pointing to a new therapeutic approach. Depending on the observer's standpoint, either the nonresponders in clinical trials testify to the inefficacy of these agents, or the responders bear out their activity. This controversy has severely hindered genuine scientific progress and has prevented full advantage from being taken of the therapeutic potential of the nootropics.

Piracetam is long since not the sole representative of this class. In the meantime a great many structurally related active compounds have been synthesized, confirming the need to assign the nootropics to a category of their own. The term *nootropic* derives from the Greek words *noos*, mind, and *tropos*, toward, and thus reflects not a class of chemical structures, but the supposed effect of these compounds on cognitive processes. It is consequently inevitable that a certain tendency exists to attach this label to all memory-enhancing substances (for a comprehensive review, see references 3,4).

The present review is devoted entirely to the piracetam-like preparations and focused on their direct nootropic effects, i.e., the spectrum of effects on the memory of intact animals, rather than on their mechanism of action. The latter aspect was the subject of recent reviews.[4,5] Since it is impossible to assess the activity of a substance without recourse to reference compounds, both the preclinical and the clinical results are discussed on that basis. Tacrine, the only compound registered for the treatment of Alzheimer's disease, is taken as the sole reference drug for comparisons of the clinical results.

II. PRECLINICAL EFFECTS OF THE NOOTROPICS

Although the first observed effect of piracetam on the central nervous system (CNS) was inhibi-

1045-4403/96/$5.00

tion of central nystagmus in the rabbit.[1] further findings made during the past 25 years showed that its main action consists in the improvement of cognitive functions. The earliest studies were concerned with pharmacological modulation of the amnesiogenic effects of a cerebral electroshock. When Giurgea and Mouravieff Lesuisse[6] demonstrated that piracetam reduced the disrupting influence of an electroshock on the orientation of rats in a water maze, this effect was taken as an indication that piracetam improved memory consolidation. Over the years, this antiamnestic action of the piracetam-like preparations has often been confirmed. Studies with aniracetam,[7] oxiracetam,[8] pramiracetam, and a series of analogues[9] all showed a distinct protective action against the effect of electroshock on memory.

This rather indirect indication of a nootropic action was supplemented and reinforced by findings showing a direct memory-enhancing effect. A great many results emerged from experiments in avoidance learning. For example, aniracetam and piracetam[10,11] and oxiracetam[12] were found to exert direct effects on the acquisition and retention performance of rats and mice in both passive- and active-avoidance paradigms. Of particular value were the results of investigations in which the preparations were administered immediately after the learning trial ('post-trial'). In such conditions, the animal experiences the learning situation without being under the influence of the drug and is likewise uninfluenced during the retention test. Any demonstrable effect can then be ascribed to a direct action of the substance on memory processes that outlast the learning situation for some time. Several experiments showed that nootropics can improve the memory under such conditions.[13,14]

The learning situations in which piracetam-like nootropics were active were not limited to experiments involving avoidance behavior. Pramiracetam had positive effects in a place navigation task[15] and was also found to improve the acquisition rate in a 16-arm radial maze,[16] whereby the effect related exclusively to reference memory, not working memory. A slight, but significant, effect of pramiracetam was also demonstrable in a delayed alternation trial.[17] Aniracetam likewise displayed positive effects in a radial maze[18] and a matching-to-sample test.[19] Moreover, it was found that piracetam and pramiracetam improved performance in an object recognition test.[20] Aniracetam[21] and oxiracetam[22] were observed to have positive effects in a social-recognition test in rats.

In sum, from the data so far available it can be concluded that the nootropics exert a distinct memory-enhancing effect in various learning situations and in different animal species. In most experiments the acquisition or storage of the information occurred under the influence of the drug and retention was assessed after an interval of at least one day. Effects on short-term retention have been described (e.g., in a delayed-alternation or delayed matching-to-sample task, and social recognition after short intervals), but these observations have not yet been confirmed.

A. Which Memory Processes Are Facilitated by Nootropics?

The many experimental situations in which nootropics have been asserted to exert a memory-enhancing action raise the question whether there is a common denominator underlying all these effects: such as a similar target process, or whether even the whole spectrum of activity of the nootropics is the same. The available evidence would suggest that their activity spectra are not identical, but at least very similar, inasmuch as all these preparations improve passive avoidance[23,24] and active avoidance,[12,25] and all of them improve retention performance, even if administered post-trial.[13] The results of studies with post-trial administration reveal a high degree of concordance: it has been demonstrated that all four prototype nootropics—oxiracetam, piracetam, pramiracetam, and aniracetam—can enhance memory even if administered up to eight hours after the learning trial. After an interval of 16 hours, an effect was no longer evident.[13,14] It can be inferred that under these conditions all these drugs affect a process that outlasts the learning situation by more than 8, but less than 16, hours (a hypothesis relative to the process affected is advanced in reference 14). The improvement in retention performance in all these experiments was assessed after 24 or 72 hours, i.e., at a time when the memory content is generally supposed to be

present in a long-term form. It was further shown that the retention performance of mice exposed to a learning situation after receiving a single dose of oxiracetam was distinctly better than that of controls even after one, two, or four months.[26] This finding lent additional support not only to the assumption that the substances ultimately improve long-term memory (LTM) storage, but also to the supposition that after intervals of 1 to 120 days memory is based on the same substrate.

Also in accord with the hypothesis that the nootropics improve LTM storage are the responses evoked by pramiracetam[16] and aniracetam[18] in the radial maze, in which solely effects on reference memory were observed. Thus, the only effects remaining to be explained are those noted in the delayed matching-to-sample test[18] and the improvements seen in the social-recognition test after a two-hour interval.[21] If these effects hold good for all nootropics, they can be taken as an indication that the facilitation of LTM is just one aspect of a whole range of activity; if not, they could indicate differences in the activity spectra of the various nootropics. Many indications of differences have been observed. Comparative studies of pramiracetam and etiracetam, for example, showed that only etiracetam had effects on memory retrieval.[27] Moreover, a long list of experiments indicate quantitative and qualitative differences in the biochemical activity spectrum of piracetam-like nootropics[4,28–30] so that there is hardly cause to expect such drugs to display an identical spectrum of activity.

Thus, the most obvious common feature of the nootropics is their capacity to facilitate LTM storage. This conclusion is consistent with the majority of the available preclinical results. Despite the high degree of similarity in the observed effects, some experimental findings do appear to indicate differences in the activity spectra.

B. Effects of Nootropics Compared with Those of Other Memory Enhancers

Comparative studies have revealed that there are no differences among the LTM effects of the four prototype nootropics—oxiracetam, piracetam, aniracetam, and pramiracetam—the cholinomimetics—tacrine, physostigmine, and arecoline—the ACE inhibitor captopril, the calcium antagonist nimodipine, and the gamma-aminobutyric acid B (GABAB)-receptor antagonist CGP 36742 in a passive-avoidance paradigm (Figure 1). It was subsequently observed that all these LTM effects were equally steroid sensitive; i.e., experimentally elevated aldosterone or corticosterone levels suppressed the effects of all these memory enhancers to the same extent.[23,31] The pharmacodynamics of oxiracetam, arecoline, CGP 36742, and captopril were similar: there was an 8-hour drug-sensitive window after the learning trial (Figure 2). Note that the memory-enhancing effects induced by captopril, CGP 36742, and the muscarinic cholinergic agonist arecoline followed almost exactly the same pattern as that of oxiracetam, in that they were not immediately detectable, i.e., not in evidence as soon as the animals showed signs of retention. At least a further 16-20 hours elapsed before it emerged (Figure 3). This surprising concordance in the findings strongly suggests that all four of these drugs affect the same process.

By analogy with the results obtained with oxiracetam, it seems reasonable to assume that the process in question is LTM storage. This conclusion is proposed purely as a possible common denominator and must not be construed as an exhaustive description of the activity spectrum. The totality of the cholinergic effects induced by physostigmine activates the brain quite differently from blockade of the angiotensin-converting enzyme or the effects of piracetam. It is consequently logical that, despite the common effects, differences in the activity spectra are to be expected. Such differences have been observed in experimental studies: only captopril facilitated memory retrieval after a 2-month retention interval; piracetam did not.[32] Piracetam and pramiracetam improved performance in an object recognition test,[20] whereas physostigmine had no such effect.[33] In contrast to pramiracetam,[16] and aniracetam,[18] physostigmine had no memory-enhancing effect in radial-maze tests.[33] It must, however, be conceded that these results are not derived from comparative studies.

In summary, all memory-enhancing compounds display similarities in their activities and in the intensities and dynamics of their effects in LTM experiments. The effects are steroid sensitive and become detectable only after a lapse of

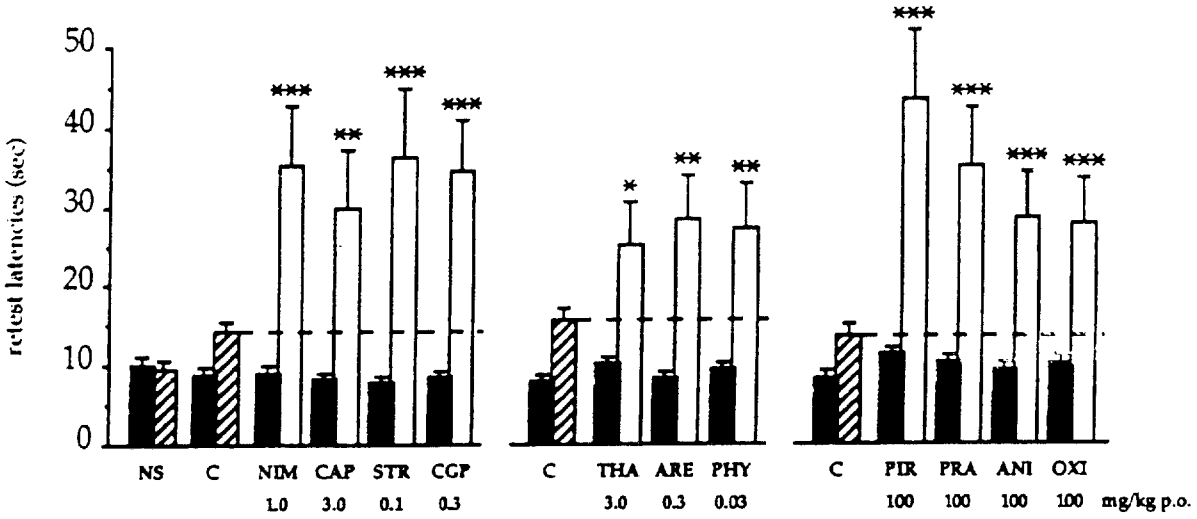


FIGURE 1. The effects of various memory-enhancing substances on the retention performance of mice in a passive-avoidance task. Mice were given footshock for leaving a "safe" small platform in the center of a grid floor. The spontaneous ("baseline") latencies to step onto the grid were measured. Retention (i.e., the retest latencies) was assessed 24 hours later. The histograms represent the step-down latencies in seconds. Solid columns: baseline latencies; blank columns: retest latencies of drug-treated animals; hatched columns: retest latencies of the vehicle-treated controls. NIM: nimodipine; CAP: captopril; STR: strychnine; CGP: CGP 36742 (GABAB antagonist); THA: tacrine; ARE: arecoline; PHY: physostigmine; PIR: piracetam; PRA: pramiracetam; ANI: aniracetam; OXI: oxiracetam. Physostigmine was given orally 30 minutes, all other substances, two hours, before the learning trial. Optimal doses for memory improvement were determined in independent pilot experiments. Prolongation of the retest latencies (in comparison with the no-shock controls [NS] and baseline latencies) indicates learning. Prolongation of the retest latencies in comparison with the retest latencies of the vehicle-treated controls indicates drug-induced memory improvement. N = 25 mice/group. $^{*}2p<0.05$, $^{**}2p<0.01$, $^{***}2p<0.001$ (Mann-Whitney U-test)

several hours. There are, nevertheless, experimental findings indicating differences in activity spectra, both within and between the various groups of memory enhancers, above all in tests not related to LTM.

III. THE CLINICAL EFFECTS OF THE NOOTROPICS

Any attempt to pinpoint common features in the available clinical data on these compounds quickly runs into certain problems. One major difficulty is due to the heterogeneity of the patient populations. Studies have been carried out in probable cases of Alzheimer's disease,[34–38] in a mixed population of Alzheimer and multiinfarct dementia patients, [ ] in multiinfarct patients,[43] in patients with psychoorganic syndrome,[44–48] in aged volunteers,[49] in students,[50] in epileptic patients,[51] in dyslexic schoolchildren,[52] in patients suffering from effects of exposure to organic solvents,[53,54] in victims of head trauma,[55,56] in patients with Korsakoff's syndrome,[57] and even in patients with artificial pacemakers.[58] The numbers of patients in each study ranged from 4[56] to 289.[41] Durations of treatment also varied greatly: for example, 9 days,[58] 4 weeks,[43,45] 3 months,[39–41,46,47,51] and up to 1 year.[34] The study design was variously open,[59,60] single-blind,[43,61] double-blind,[34,39,40] parallel with placebo controls[36,39,41,42] or active controls,[62,63] crossover,[37,54] or enriched;[35] even comparisons with historical controls were used.[64]

No less heterogeneous was the clinical and psychometric instrumentarium employed to assess the effects. Besides neuropsychological tests and scales, psychophysiological tests were also used. The quality of reporting differed greatly. In some studies, the test used is not simply mentioned but described exactly (e.g., reference 40), whereas in others the sole indication of the nature of the effect observed and the methodology applied was the single word *memory*.[63] In evaluating the effects, the psychometric tests were some-

times supplemented by staff-rated scales[47]; sometimes only staff-rated scales were used,[65] or even ...st the clinician's global impression was given.[66] The study design was entirely adapted to demonstrating the existence of an effect of the preparation in patients.

Surprisingly, at first glance, scrutiny of the results of the published clinical studies reveals that the majority (more than 60%) of the reports are positive; i.e., the authors conclude from their findings that the treatment was effective. Villardita et al.,[39] for instance, showed that after three months the 30 patients treated with oxiracetam in a double-blind, parallel-design study displayed significant improvements in 9 of the 18 tests used compared with their baseline performance before the beginning of treatment. The 30 placebo-treated patients, on the other hand, showed no improvements, and even performed significantly worse in two of the tests. The positive effects were particularly clear-cut in the Mini Mental State Examination (MMSE), the Auditory Continuous Performance Test (ACPT), Rey's 15 Words Test, the Block Tapping Test (BTT), the Mattis Word Fluency Test, Luria's Alternating Series, and the Instrumental Activities of Daily Living Test (IADL-E).

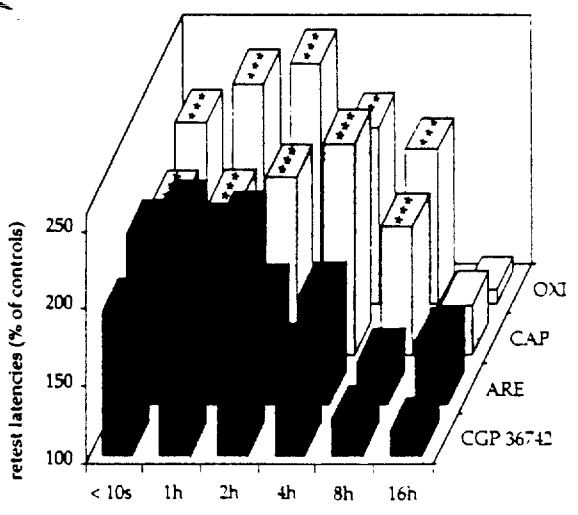


FIGURE 2. The effects of various compounds on memory if administered at various intervals after the learning experience. The animals were exposed to the passive-avoidance situation, and after the indicated intervals (<10 seconds, 1, 2, 4, 8, 16 hours) treated with optimal doses of the memory enhancers. Retest was performed after 72 hours. The columns indicate the prolongation of the retest latencies (in percent of the vehicle-treated matched controls). Prolonged latencies indicate better memory. ARE: arecoline; CAP: captopril; OXI: oxiracetam. *2p<0.05, **2p<0.01, ***2p<0.001.

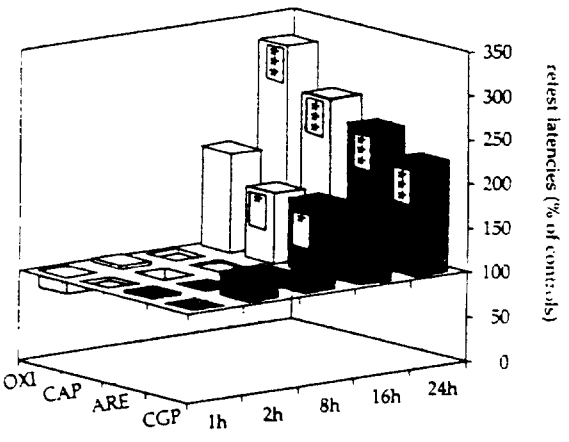


FIGURE 3. The emergence of the memory facilitation effect induced by the nootropic oxiracetam (100 mg/kg), the ACE-inhibitor captopril (3 mg/kg), the muscarinic agonist arecoline (0.3 mg/kg), and the GABAB-receptor blocker CGP 36742 (10 mg/kg). The animals were trained in a passive-avoidance situation and treated immediately thereafter. Retention performance was measured at various intervals (1, 2, 8, 16, or 24 hours) after training and treatment. The columns indicate the drug-induced prolongation of the retest latencies (in percent of the vehicle-treated controls). *2p<0.05, **2p<0.01, ***2p<0.001. Prolonged latencies indicate better memory. All treatments were given intraperitoneally immediately after the learning trial (from Mondadori et al., *Proc. Natl. Acad. Sci.*, 91, 2041, 1994).

Senin et al.[38] performed a study with aniracetam, using a test battery different from that applied by Villardita. At the end of the 6-month treatment period the authors found significant improvements of performance in all 18 parameters assessed. As in Villardita's study, positive effects were recorded in Rey's 15 Word Test. Note that besides effects on cognitive parameters, these authors also observed distinct effects on behavioral parameters. The 6-month study with aniracetam performed by Parnetti et al.[67] according to a similar design yielded practically identical results: in 17 of 18 tests, aniracetam improved the patients' performance. In this comparative study the activity spectrum of aniracetam in some tests was distinctly different from that of piracetam. Unlike aniracetam, for instance, piracetam displayed no effects in Rey's 15 Words Test, in the Toulouse Pieron Test, and in the

Raven Test. According to the Sandoz Clinical Assessment Geriatric (SCAG) Scale, however, the effects were nearly identical. Bottini et al.[40] observed distinct effects of oxiracetam in five of eight cognitive tests. In particular, there were significant positive effects on verbal fluency, similar to those described by Villardita et al., and the retention of a short story (after a delay of 10 minutes) was also improved. In the 12-month study with piracetam conducted by Croisile et al.,[34] indications of a retardant effect of the drug on the progress of mental decline were noted: in the placebo group a significant deterioration was evident at the end of the year in 8 of 14 tests, whereas in the piracetam group negative results were recorded in only one test. In contrast to the findings of Senin et al. and Parnetti et al., direct comparisons of the performance of placebo-treated and piracetam-treated patients yielded scarcely any statistically significant results. The study carried out by Maina et al.[41] in the largest population samples of all (N = 144 + 145), positive (good to very good) effects of oxiracetam were recorded in 90 of 145 patients (global evaluation), whereas, according to the same criteria, only 27 of 144 placebo-treated patients were rated as showing good or very good responses. Only 51 of 144 patients taking oxiracetam as against 107 of 144 receiving placebo were rated as showing no effect or a poor effect. Note that the patients in this study, in contrast to those in the study by Villardita et al., showed positive effects in the IPSC-E (Inventory of Psychic and Somatic Complaints, Elderly). Statistically significant increases in the IPSC-E scores were also recorded in the 6-month study performed by Mangoni et al.,[36] while no changes were seen in the placebo-treated controls.

Itil et al.[46] also reported significant effects of oxiracetam in the IPSC-E, not in Alzheimer patients, but in diagnostically less precisely defined cases of organic brain syndrome (OBS). These effects were more pronounced than the corresponding effects of piracetam. Such changes in the IPSC-E suggest that oxiracetam exerts effects that can be manifest as an improvement in the quality of life of the patients. The results obtained by Saletu et al.[45] in their study of a similar patient population were far less distinct: apart from an improvement in verbal memory, only the overall score in the SCAG was significantly better (the IPSC-E was not used). The duration of treatment in this study was only four weeks. More modest still were the clinical effects noted in the study of piracetam performed by Abbuzahab et al.[48] in OBS patients (geriatric memory): apart from a slight overall improvement, no relevant effects were observed. Much more pronounced positive effects emerged from the investigation by Moglia et al.[42] In this parallel-design study in 21 + 22 OBS patients, these authors showed that oxiracetam induced an overall improvement in cognitive and behavioral parameters. Particularly notable were the significant improvements seen in the Benton Visual Motor Retention test (as also used by Itil et al.) and in the arithmetical part of the Wechsler Adult Intelligence Scale (WAIS). The conclusion that the general well-being of the patients treated with oxiracetam had improved is consistent with the many global clinical assessments, as exemplified by a 3-month placebo-controlled study in 60 patients with two doses of piracetam carried out by Chouinard et al.[47] In this study, the results of the monthly evaluations by the nursing staff (Nurses Global Improvement Rating Scale) clearly indicated an improvement in the patients' sense of well-being, whereby particular emphasis was placed on alertness, socialization, and orientation. Another study by Foltyn et al.,[65] showing aniracetam to have been effective over a duration of four weeks in N = 30 +30 patients, was based exclusively on staff ratings.

Nootropics were also tested for efficacy in completely different clinical indications. McLean et al.,[56] for example, examined pramiracetam in four patients with head injuries or anoxia and showed that the drug exerted clear-cut effects on immediate and delayed recall. In patients with pacemakers, in whom the fixed heart rate often leads to diminished cerebral circulation and consequent disturbances of performance during exertion, piracetam was found to induce a slight improvement in psychomotor tests[58]; no cognitive tests were performed, however. In a study in epileptic patients with memory disorders, Aldenkamp et al.[51] observed no effects after 12 weeks, but all parameters measured revealed a trend favoring oxiracetam.

In some investigations, comparative evaluations were made of the effects of nootropics. In

the above-mentioned study by Itil et al.,[46] oxiracetam was found to have a slightly better effect on cognitive parameters than piracetam, whereas piracetam displayed a slightly better antipsychotic effect than oxiracetam. Although the greater efficacy of oxiracetam in regard to cognitive aspects was confirmed in the studies by Gallai et al.[61] and Ferrero,[63] these studies were not carried out under double-blind conditions and are consequently not admissible as valid scientific evidence. The same applies to the study conducted by Falsaperla,[62] in which the effects of oxiracetam were compared with those of deprenyl in Alzheimer patients. Here, both drugs improved the patients' performance above baseline levels in a whole series of tests, deprenyl emerging as the more effective treatment. Aniracetam was also shown to be slightly more active than piracetam in the study by Parnetti et al.[67]

In contrast to the many positive results reported, a 3-month study in Alzheimer patients performed by Green et al.[68] and using a broad battery of neuropsychological tests revealed no signs of efficacy of oxiracetam, either on the basis of group analyses or in individual patients. Similarly, a 3-month trial by Hjorther et al.[53] with a very extensive test battery gave no indication of any effects of oxiracetam: neither behavioral nor memory parameters showed any signs of improvement. Note that this trial was done in a special group of OBS patients, suffering from toxic encephalopathy following exposure to organic solvents. In full concordance with these results, Somnier et al.[54] detected no signs of efficacy of aniracetam in such patients. A notable feature of this study was that Somnier employed a crossover design. Other crossover trials have also revealed no positive effects. Lloyd-Evans et al.[44] were unable to detect any effects of piracetam in a 6-month double-blind trial in OBS patients. The 2 × 4-week crossover study with oxiracetam performed by Molloy et al.[37] in Alzheimer patients likewise showed no effects. In none of these crossover trials was the first drug/placebo phase evaluated separately as a parallel study. Negative results further emerged from an enriched-design study by Claus et al.,[35] who concluded from their results that pramiracetam is ineffective as a symptomatic treatment for Alzheimer patients. This rating was based on the scores achieved by 10 patients in the Alzheimer's Disease Assessment Scale (ADAS). In patients with alcoholic organic mental disorders also, a study conducted by Fleischhacker et al.[57] demonstrated no relevant improvement after treatment with piracetam.

Given the existence of studies with positive and others with negative results or overall ratings, one question that arises is what 'positive' or 'negative' means to the individual patients. As regards the positive studies, that question has already been answered, insofar as it was often mentioned that only a limited number of patients responded to the treatment (e.g., reference 41). Unfortunately, in the clinical studies with nootropics, only scant information is given about the frequency of significant therapeutic effects and the quality of such effects in individual patients. The fact that, despite many nonresponders, positive overall ratings were still reported would at least seem to justify the reverse question of how often individual responders were present even in the negative studies. For want of adequate information on responders and nonre-sponders in most double-blind studies, illustrative data must also be drawn from the results of open trials. In the study performed by Claus et al.,[35] the conclusion that piracetam was ineffective was based on the lack of significant effects in the ADAS in 10 patients. In fact, however, there was at least one responder with a reduction of more than four points in the ADAS and significant drug-related improvements in both the Visual Selective Reminding Task (total and delay) and Logical Memory Immediate Recall. These effects were inevitably submerged in the calculations of the means values and statistical analysis. In the study by Baumel et al.[42] also, where the drug effects were rated as very modest, 4 of the 12 patients showed responses. In that the case reports were described as typical, this was a substantial effect from the viewpoint of the quality of life. This outcome is closely similar to the results of the open study in six patients by Dager et al.,[59] in which there was one definite responder. Irrespective of the extent to which the cited data were attributable to drug effects, they demonstrate the need for analyses of this nature.

It can be concluded that the piracetam-like nootropics can evoke significant effects in Alzheimer patients, becoming manifest on the

one hand in cognitive improvements and on the other in behavioral aspects. The effect appears to become more marked during prolonged treatment. The various nootropics differ in their activity spectra. In general, however, there were only a limited number of responders. The few efforts made to characterize this group of patients (e.g., reference 59) were unsuccessful.

IV. COMPARISON WITH THE CLINICAL EFFECTS OF TACRINE

Any attempt to characterize the clinical effects of the nootropics almost automatically necessitates a comparison with cholinomimetics. In contradistinction to the nootropics, cholinergic substances are used in Alzheimer patients, not because of their memory-enhancing effects in animals, but because of the existence of a cholinergic deficit in these patients.[69] In this respect, the patient population studied is homogeneous and, unlike the very mixed populations treated with nootropics, includes only (probable) Alzheimer patients. The group sizes are similar to those in the nootropic studies. The methodology used is more nearly uniform but different from that adopted for nootropics. The following section is confined to tetrahydroaminoacridine (THA, tacrine, Cognex®), a cholinesterase inhibitor and the only substance so far registered for the treatment of Alzheimer's disease.

The first study by Summers et al.[70] was conducted in three phases. In the first phase, the tolerability and efficacy of incremental doses of THA were assessed in 23 patients. THA was always administered in combination with lecithin. In a second double-blind, crossover phase, 15 of these patients were treated with the best or highest dose of THA, or with placebo, for three weeks, after which the treatments were switched. Only the 12 patients showing a clear-cut response to THA in the second phase went on to receive long-term treatment over periods ranging from 3 to 26 months (enriched design). The final assessment revealed distinct positive results (global assessment, orientation, Alzheimer deficit scale, names learning test), whereby only patients classed as Stages 3-4, but not Stages 5-6, on the Reisberg scale responded.

Most of the subsequent studies initially failed to confirm Summers' results. A crossover study conducted by Davies et al.,[71] for example, in which 10 patients were treated for up to four months, showed hardly any notable effects of the combined treatment with THA and lecithin. Only in 1 of 10 tests were positive results recorded. The same results were obtained by Chatellier et al.[72] In this crossover study with 67 patients, tacrine (combined with lecithin) was administered orally for four weeks. Apart from a slight improvement in the Physician's Score, THA was ineffective. Neither in behavioral scales (Stockton) nor in cognitive scales (MMSE) were any effects demonstrable. Similarly, in a crossover trial done by Gauthier et al.[73] over two 8-week treatment periods, the response to THA was limited to an improvement in the MMSE. Despite this improvement, the authors rated the effect of THA as clinically irrelevant. No effect whatever was observed by Molloy et al.[74] in a multiple crossover study with treatment periods of three weeks. Neither the overall evaluation nor a detailed analysis of individual patients revealed any indications of effects.

Positive results, on the other hand, were obtained in the trial conducted by Davis et al.[75] The 215 patients who had responded to tacrine in a preliminary crossover phase were subsequently treated for six weeks in a parallel study. By comparison with the placebo controls, the tacrine group showed a slight, but significant, decrease in mental decline (ADAS cognitive subscale). Two of the three quality-of-life assessment scales used indicated changes in favor of tacrine: Progressive Deterioration Scale (PDS) and Activities of Daily Living (ADL). The changes in the MMSE were slight and statistically not significant, and the clinician's global assessment (CGIC) likewise failed to detect any effects. In a similar, but more prolonged (12-week) parallel study by Farlow et al.,[76] very much the same results were obtained: the ADAS cognitive subscale indicated some retardation of cognitive decline, but the MMSE showed no changes. In contrast to the study by Davis, however, the physicians' and caregivers' global ratings were significantly better. In a crossover study by Eagger et al.,[77] in which 468 patients were treated for considerably longer (13 weeks) than those in Molloy's study,[74] the MMSE

and the AMTS (Abbreviated Mental Test Score), but not the ADL, revealed an effect of tacrine. The effects in the MMSE were consistent with the findings of Gauthier et al.,[73] but not with those of Farlow et al.[76] and Davis et al.[75]; the absence of effects in the ADL were at variance with the results observed by Davis et al.[75]

Recent studies disclosed the entire range of possible effects. Distinctly positive effects emerged from a 30-week parallel study by Knapp et al.[78] In this study with an initial population of 663 patients, all three primary outcome measures (ADAS cognitive subscale, Clinicians' Interview-Based Impression, and Final Comprehensive Consensus Impression) showed significant effects of tacrine. In addition, positive effects, among others, were demonstrated by the Progressive Deterioration Scale and the MMSE, but not the ADL. The effects indicated by the MMSE were in agreement with those noted by Gauthier et al.,[73] Eagger et al.,[77] and Davis et al.,[75] but contrary to those seen by Farlow et al.[76] and Molloy et al.[74] Although consistent with the findings of Eagger et al.,[77] the absence of effects in the ADL conflicted with those of Davis et al.[75] Exactly the opposite, i.e., no indications of any effect whatever, emerged from the study by Maltby et al.[79] with an initial population of 57 patients and a 36-week duration of treatment. Neither the Caregivers' rating-based scales nor the cognitive scales showed signs of changes. Halfway between positive and negative results lie the findings reported by Wilcock et al.[80] In a 2 × 3-month crossover study in 41 patients these authors noted positive trends in favor of tacrine, but statistically the differences were scarcely significant. In a study with 154 patients, Wood et al.[81] likewise merely observed positive trends, but there was no significant effect of tacrine in the overall group analysis. The results nevertheless indicate that there were individual responders. The same applies to a 3 × 6-week crossover study of Alzheimer patients conducted by Gustafson[82] in which there was no detectable overall effect, but individual responders were noted. It is, above all, the enrichment studies that confirm the existence of a subset of responders, although even after the enrichment not all patients respond to the treatment. In the light of these findings and in view of the need to optimize the therapy, it is surprising that scarcely any efforts have been made to establish a pharmacological, biochemical, and endocrinological profile that would serve to identify likely responders.

To sum up, although there are clear indications that cholinesterase inhibitors do exert clinical effects, it is equally clear that only a certain number of patients respond to the treatment. The use of enriched-design studies often makes the proportion of responders appear larger than it really is. As with nootropics, longer durations of therapy improve the chances of evoking demonstrable effects. The psychometric scales and tests employed were in most cases not comparable with those used in the nootropic trials. In the few studies in which comparable scales and tests (MMSE, ADL) were used, the effects observed were of roughly the same magnitude as those produced by the nootropics. Although the methodology was much more nearly uniform than in the nootropics studies, there was no test that yielded consistently positive results in all trials.

V. PRECLINICAL EFFECTS OF THE NOOTROPICS IN THE LIGHT OF CLINICAL FINDINGS

Before considering the extent to which the clinical data meet the expectations based on preclinical findings, I must stress once again that the clinical investigations were exclusively aimed at showing whether or not the preparations exerted any therapeutic effects. For that reason a wide battery of tests was used, comprising both behavioral aspects and cognitive performance. The somewhat unfortunate efforts of many authors to make use of data from animal experiments in explaining the rationale of their studies and discussing the clinical results should not be allowed to obscure the fact that neither were the studies designed to validate the preclinical results, nor were the clinical results in any way adjusted to serve that purpose.

In the vast majority of the preclinical studies, a design was used in which the experimental animals were exposed to the learning situation while under the influence of the drugs and then tested for retention 24 hours later, either still, or no longer, under the influence of the drugs. In the clinical studies, however, retention performance was tested after short-term intervals, i.e., either

immediately after acquisition or after a lapse of 10 minutes. The several hours' delay preceding the emergence of detectable memory-facilitating effects that has been observed in the most recent animal experiments[4,24] strongly emphasizes the crucial importance of allowing long enough retention intervals, provided only, of course, that the clinical effect and the memory facilitation observed in animals come about by way of the same mechanism. What the long-term memory tests used in the clinical studies detected was not the influence of the substances on long-term storage, but their influence on retrieval from LTM, i.e., on the recall of information acquired while not under the influence of the drugs. Often, learning capacity was tested before and at the end of the treatment period: i.e., performance without the influence of the drugs was then compared with performance while under the acute influence of the drugs. There is thus still no sound scientific evidence of the predictive validity of the animal procedures. This aspect should be examined in specifically designed clinical investigations.

The various reports nevertheless do contain at least a few allusive remarks consistent with the expectations based on animal experiments. In the study with oxiracetam by Dager et al.,[59] for example, there is a sentence reading: "although long term recall improved only negligibly, his long term memory storage (learning capacity) and recognition memory were moderately enhanced." Similarly McLean et al.[56] state that: "The most dramatic demonstration of improvement with pramiracetam ... occurred in the selective reminding test-delayed recall, long term memory retrieval and long term storage." Last, but not least, there are a number of reports concerning the effects of piracetam in dyslexic children that possibly point to effects on LTM storage. In a double-blind, placebo-controlled study by Wilsher et al.[52] the children showed greater facility in reading and comprehension after a 36-week phase of treatment with piracetam. It is very probable that the improved performance at the end of the treatment period reflects, not an acute effect on memory retrieval, but rather an improved availability of the knowledge acquired throughout the duration of treatment, i.e., long-term retention of information acquired under the influence of piracetam. This view is strongly supported by the fact that the combination of psychological training and nootropic therapy proved particularly effective, not only in dyslexic children, but also in other forms of cognitive underperformance.[33] Moreover, it appears very likely that the effects observed after long-term treatment of Alzheimer patients might, at least partially, be based on such effects, too.

However, the many reports on an improvement in noncognitive aspects in individual studies or patients make it seem improbable that nootropics act exclusively on LTM storage. It is conceivable that the effect comes about via a modification of general processes that play an important role in the performance of brain cells. The improvement in long-term storage would then be only one of the measurable consequences. The reason for the usually modest extent of the clinical effects could be that the action of the substances is confined to cells that are still functionally competent. But since the individual patient's specific pattern of functional deficits reflects the impairment of the neuronal circuits essential to this function, it may be that the aspect most impaired through degeneration also affords the least room for improvement. This applies equally to cognitive and noncognitive performances. It is therefore perfectly conceivable that while measurable effects in one aspect or another may be detectable in a wide-ranging psychometric investigation, these aspects may be of little therapeutic relevance to the symptoms that are particularly disabling for the patient.

VI. SYNTHESIS AND OUTLOOK

Given the observed overall positive effects of the nootropics and their occasionally quite distinct effects in individual patients, this category of compounds would appear useful. The results available so far give no indication that tacrine is superior to the nootropics, or vice versa. The effects of these drugs seem to be similar, although the complication that the double-blind nature in connection with cholinomimetics is very probably wishful thinking (dicriminative stimulus properties,[84] side effects, e.g., reference 74) has been completely left out of consideration. In the absence of comparative studies, the tacit assump-

tion that the cholinomimetics are more effective most likely reflects the superficial plausibility of the underlying hypothesis rather than the existing clinical results. Together, the clinical results present a mirror image of the preclinical profile.

In order to maximally exploit the available therapeutic possibilities, it would be desirable to give priority to the characterization of a subgroup of patients likely to respond to a particular therapy. The steroid dependence of the memory-facilitating effect of the nootropics[23,31] opens up a practical possibility in view of the fact that a very large percentage of Alzheimer patients have elevated plasma cortisol concentrations.[85] This approach would, of course, be valid only if the memory-enhancing effects seen in preclinical studies and the effect observed in patients come about by way of the same mechanism. This brings us back to the question of the validity of the preclinical models, which urgently need clarifying by clinical trials specifically designed for that purpose.

REFERENCES

1. **Giurgea, C. E., Moyensoons, F., and Emand, A. A.,** A Gaba-related hypothesis on the mechanism of action of the anti-motion sickness drugs, *Arch Int. Pharmacodyn.*, 166, 379, 1967.
2. **Giurgea, C. E.,** The 'nootropic' approach to the pharmacology of the integrative activity of the brain, *Conditional Reflex*, 8, 108, 1973.
3. **Fröstl, W. and Maître, L.,** The families of cognition enhancers, *Pharmacopsychiatry*, 22 (Suppl.), 54, 1989.
4. **Mondadori, C.,** In search of the mechanism of action of the nootropics: new insights and potential clinical implications, *Life Sci.*, 55, 2171, 1994.
5. **Vernon, M. W. and Sorkin, E. M.,** Piracetam: an overview of its pharmacological properties and a review of its therapeutic use in senile cognitive disorders, *Drugs & Aging*, 1, 17, 1991.
6. **Giurgea, C. E. and Mouravieff-Lesuisse, F.,** Effet facilitateur du piracetam sur un apprentissage répétuif chez le rat, *J. Pharmacol.*, 3, 17, 1972.
7. **Cumin, R., Bandle, E. F., Gamzu, E., and Haefely, W. E.,** Effects of the novel compound aniracetam (Ro 13-5057) upon impaired learning and memory in rodents, *Psychopharmacology*, 78, 104, 1982.
8. **Banfi, S. and Dorigotti, L.,** Experimental behavioral studies with oxiracetam on different types of chronic cerebral impairment, *Clin. Neuropharmacol.*, 9, 19, 1986.
9. **Butler, D. E., Leonard, J. D., Caprathe, B. W., L'Italien, Y. J., Pavia, M. R., Hershenson, F. M., Poschel, P. H., and Marriott, J. G.,** Amnesia-reversal activity of a series of cyclic imides, *J. Med. Chem.*, 30, 498, 1987.
10. **Yamada, K., Inoue, T., Tanaka, M., and Furukava, T.,** Prolongation of latencies for passive avoidance responses in rats treated with aniracetam or piracetam, *Pharmacol. Biochem. Behav.*, 22, 645, 1985.
11. **Mondadori, C. and Petschke, F.,** Do piracetam-like compounds act centrally via peripheral mechanisms? *Brain Res.*, 435, 310, 1987.
12. **Sansone, M. and Oliverio, A.,** Avoidance facilitation by nootropics, *Prog. Neuropsychopharmacol. Biol. Psychiatry*, 13, 89, 1989.
13. **Mondadori, C., Ducret, T., and Borkowski, J.,** How long does 'memory consolidation' take? New compounds can improve retention preformance, even if administered up to 24 hours after the learning experience, *Brain Res.*, 555, 107, 1991.
14. **Mondadori, C., Hengerer, B., Ducret, T., and Borkowski, J.,** Delayed emergence of effects of memory-enhancing drugs: implications for the dynamics of long-term memory, *Proc. Natl. Acad. Sci.*, 91, 2041, 1994.
15. **Poschel, B. P. H., Ho, P. M., Ninteman, F. W., and Callahan, M. J.,** Pharmacologic therapeutic window of pramiracetam demonstrated in behavior, EEG, and single neuron firing rats, *Experientia*, 41, 1153, 1985.
16. **Murray, C. L. and Fibiger, H. C.,** The effect of pramiracetam (CI-879) on the acquisition of a radial arm maze task, *Psychopharmacology*, 89, 378, 1986.
17. **Poschel, B. P. H., Marriott, J. G., and Gluckman, M. I.,** Pharmacology of the cognition activator pramiracetam (CI-879), *Drugs. Exp. Clin. Res.*, IX, 853, 1983.
18. **Martin, P. R., Cumin, R., Aschwanden, W., Moreau, J. L., Jenck, F., and Haefely, W. E.,** Aniracetam improves radial maze performance in rats, *NeuroReport*, 3, 81, 1992.
19. **Pontecorvo, M. J. and Evans, H. L.,** Effects of aniracetam on delayed matching-to-sample performance of monkeys and pigeons, *Pharmacol. Biochem. Behav.*, 22, 745, 1985.
20. **Ennaceur, A., Cavoy, A., Costa, J. C., and Delacour, J.,** A new one-trial test for neurobiological studies of memory in rats. II: effects of piracetam and pramiracetam, *Brain Res.*, 33, 197, 1989.
21. **Perio, A., Terranova, J. P., Worms, P., Bluthe, R. M., Dantzer, R., and Biziere, K.,** Specific modulation of social memory in rats by cholinomimetic and nootropic drugs, by benzodiazepine inverse agonists, but not by psychostimulants, *Psychopharmacology*, 97, 262, 1989.
22. **Mondadori C, Lederer R. and Zingg M.,** Delayed emergence of oxiracetam-induced facilitation of long-term memory in the social-recognition test in rats, *Psychopharmacology*, in revision, 1996.
23. **Mondadori, C., Ducret, T., and Häusler, A.,** Elevated corticosteroid levels block the memory-improving effects of nootropics and cholinomimetics, *Psychopharmacology*, 108, 11, 1992.

24. **Mondadori, C.,** The pharmacology of long-term memory, *Eur. Rev.*, 3, 35, 1995.
25. **Kuribara, H. and Tadokoro, S.,** Facilitating effect of oxiracetam and piracetam on acquisition of discrete two-way shuttle avoidance in normal mice, *Jpn. J. Pharmacol.*, 48, 494, 1988.
26. **Mondadori, C., Möbius, H.J., and Borkowski, J.,** The GABAB receptor antagonist CGP 36 742 and the nootropic oxiracetam facilitate the formation of long-term memory, *Behav. Brain Res.*, 77, 223, 1996.
27. **Sara, S. J.,** Memory retrieval deficits: alleviation by etiracetam, a nootropic drug, *Psychopharmacology*, 68, 235, 1980.
28. **Xiao, P., Staubli, U., Kessler, M., and Lynch, G.,** Selective effects of aniracetam across receptor types and forms of synaptic facilitation in hippocampus, *Hippocampus*, 1, 373, 1991.
29. **Spignoli, G. and Pepeu, G. C.,** Interactions between oxiracetam, aniracetam and scopolamine on behavior and brain acetylcholine, *Pharmacol. Biochem. Behav.*, 27, 491, 1987.
30. **Pugsley, T. A., Poschel, B. P. H., Downs, D. A., Shih, Y.-H., and Gluckman, M. I.,** Some pharmacological and neurochemical properties of a new cognition activator agent, pramiracetam (CI-879), *Psychopharmacol. Bull.*, 19, 721, 1983.
31. **Mondadori, C., Gentsch, C., Hengerer, B., Ducret, T., Borkowski, J., Racine, A., Lederer, R., and Häusler, A.,** Pretreatment with aldosterone or corticosterone blocks the memory-enhancing effects of nimodipine, captopril, CGP 37849, and strychnine in mice, *Psychopharmacology*, 109, 383, 1992.
32. **Mondadori, C. and Etienne, P.,** Nootropic effects of ACE-inhibitors in mice, *Psychopharmacology*, 100, 301, 1990.
33. **Ennaceur, A. and Meliani, K.,** Effects of physostigmine and scopolamine on rats' performances in object-recognition and radial-maze tests, *Psychopharmacology*, 109, 321, 1992.
34. **Croisile, B., Trillet, M., Fondarai, J., Laurent, B., Mauguiere, F., and Billardon, M.,** Long-term and high-dose piracetam treatment of Alzheimer's disease, *Neurology*, 43, 301, 1993.
35. **Claus, J. J., Ludwig, M. D., Mohr, E., Giuffra, M., Blin, J., and Chase, T. N.,** Nootropic drugs in Alzheimer's disease: symptomatic treatment with pramiracetam, *Neurology*, 41, 570, 1991.
36. **Mangoni, A., Perin, C., Smirne, S., Piccolo, I., De Filippi, F., Marchetti, C., Motta, A., and Monza, G. C.,** A double-blind, placebo-controlled study with oxiracetam in demented patients administered the Luria-Nebraska neuropsychological battery, *Drug Dev. Res.*, 14, 217, 1988.
37. **Molloy, D. W., Guyatt, G., and Brown, G.,** Effects of oxiracetam on cognition, behaviour and activities of daily living in dementia, *J. Clin. Exp. Gerontol.*, 14, 217, 1992.
38. **Senin, U., Abate, G., Fieschi, C., Gori, G., Guala, A., Marini, G., Villardita, C., and Parnetti, L.,** Aniracetam (Ro 13-5057) in the treatment of senile dementia of Alzheimer's type (SDAT): results of a placebo controlled multicentre clinical study, *Eur. Neuropsychopharmacol.*, 1, 511, 1991.
39. **Villardita, C., Grioli, S., Lomeo, C., Cattaneo, C., and Parini, J.,** Clinical studies with oxiracetam in patients with dementia of Alzheimer type and multi-infarct dementia of mild to moderate degree, *Neuropsychobiology*, 25, 24, 1992.
40. **Bottini, G., Vallar, G., Cappa, S., Monza, G., Scarpini, E., Baron, P., Cheldi, A., and Scarlato, G.,** Oxiracetam in dementia: a double-blind, placebo-controlled study, *Acta Neurol. Scand.*, 86, 237, 1992.
41. **Maina, G., Fiori, L., Torta, R., Fagiani, M. B., Ravizza, L., Bonavita, E., Ghiazza, B., Teruzzi, F., Zagnoni, P. G., and Ferrario, E.,** Oxiracetam in the treatment of primary degenerative and multi-infarct dementia: a double-blind, placebo-controlled study, *Neuropsychobiology*, 21, 141, 1989.
42. **Moglia, A., Sinforiani, E., Zandrini, C., Gualtieri, S., Corsico, R., and Arrigo, A.,** Activity of oxiracetam in patients with organic brain syndrome: a neuropsychological study, *Clin. Neuropharmacol.*, 9 (Suppl.), 3, 73, 1986.
43. **Baumel, B., Eisner, L., Karukin, M., MacNamara, R., Katz, R. J., and Deveaugh-Geis, J.,** Oxiracetam in the treatment of multi-infarct dementia, *Prog. Neuropsychopharmacol. Biol. Psychiatry*, 13, 673, 1989.
44. **Lloyd-Evans, S., Brocklehurst, J. C., and Palmer, M. K.,** Piracetam in chronic brain failure, *Curr. Med. Res. Opin.*, 6, 351, 1979.
45. **Saletu, B., Linzmayer, L., Grünberger, H., and Pietschmann, H.,** Double-blind, placebo-controlled, clinical, psychometric and neurophysiological investigations with oxiracetam in the organic brain syndrome of late life, *Neuropsychobiology*, 13, 44, 1985.
46. **Itil, T. M., Menon, G. N., Bozak, M., and Songar, A.,** The effects of oxiracetam (ISF 2522) in patients with organic brain syndrome (a double-blind controlled study with piracetam), *Drug Dev. Res.*, 2, 447, 1982.
47. **Chouinard, G., Annable, L., Ross-Chouinard, A., Olivier, M., and Fontaine, F.,** Piracetam in elderly psychiatric patients with mild diffuse cerebral impairment, *Psychopharmacology*, 81, 100, 1983.
48. **Abuzzahab, F. S., Merwin, G. E., Zimmermann, R. L., and Sherman, M. C.,** A double blind investigation of piracetam (Nootropil) vs placebo in geriatric memory, *Pharmacopsychiatry*, 10, 49, 1977.
49. **Mindus, P., Cronholm, B., Levander, S. E., and Schalling, D.,** Piracetam-induced improvement of mental performance: a controlled study of normally aging individuals, *Acta Psychiatr. Scand.*, 54, 150, 1976.
50. **Dimond, S. J. and Brouwers, E. Y. M.,** Increase in the power of human memory in normal man through the use of drugs, *Psychopharmacology*, 49, 307, 1976.
51. **Aldenkamp, A. P., van Wieringen, A., Alpherts, W. C., van Emde-Boas, W., Haverkort, H. A., de Vries, J., and Meinardi, H.,** Double-blind placebo-controlled, neuropsychological and neurophysiologi-

cal investigations with oxiracetam (CGP 21690E) in memory-impaired patients with epilepsy, *Neuropsychobiology*, 24, 90, 1990.

52. **Wilsher, C. R., Bennett, D., Chase, C. H., Connors, C. K., DiIanni, M., Feagans, L., Hanvik, L. J., Helfgott, E., Koplewicz, H., Overby, P., Reader, M. J., Rudel, R. G., and Tallal, P.,** Piracetam and dyslexia: effects on reading tests, *J. Clin. Psychopharmacol.*, 7, 230, 1987.
53. **Hjorther, A., Browne, E., Jakobsen, K., Viskum, P., and Gyntelberg, F.,** Organic brain syndrome treated with oxiracetam, *Acta Neurol. Scand.*, 75, 271, 1986.
54. **Somnier, F. E., Ostergaard, M. S., Boysen, G., Bruhn, P., and Mikkelsen, B. O.,** Aniracetam tested in chronic psychosyndrome after long-term exposure to organic solvents, *Psychopharmacology*, 101, 43, 1990.
55. **Carrington Da Costa, R. B., Maul, E. R., Pimentel, J., Cardoso d'Oliveira, L., Aranjo Lacerda, J. C., and Gomes, J. D.,** A controlled clinical study. Piracetam vs placebo in disorders of consciousness due to head injuries, *Acta Ther.*, 4, 109, 1978.
56. **McLean, A., Jr., Cardenas, D. D., Burgess, D., and Gamzu, E.,** Placebo-controlled study of pramiracetam in young males with memory and cognitive problems resulting from head injury and anoxia, *Brain Inj.*, 5, 375, 1991.
57. **Fleischhacker, W. W., Günther, V., Barnas, C., Lieder, F., and Miller, C.,** Piracetam in alcoholic organic mental disorder: a placebo-controlled study comparing two dosages, *Int Clin. Psychopharmacol.*, 1, 210, 1986.
58. **Lagergren, K. and Levander, S.,** A double-blind study on the effects of piracetam upon perceptual and psychomotor performance at varied heart rates in patients treated with artificial pacemakers, *Psychopharmacologia*, 39, 97, 1974.
59. **Dager, S. R., Loebel, J. P., Claypool, K., Case, M., Budech, C. B., and Dunner, D. L.,** Oxiracetam in the treatment of primary dementia of the Alzheimer's type: a small case series, *Int. J. Geriatr. Psychiatry*, 7, 905, 1992.
60. **Branconnier, R. J., Cole, J. O., Dessain, E. C., Spera, K. F., Ghazvinian, S., and De Vitt, D.,** The therapeutic efficacy of pramiracetam in Alzheimer's disease: preliminary observations, *Psychopharmacol. Bull.*, 19, 726, 1983.
61. **Gallai, V., Mazzotta, G., Del Gatto, F., Montesi, S., Mazzetti, A., Dominici, P., and Della Monica, A.,** A clinical and neurophysiological trial on nootropic drugs in patients with mental decline, *Acta Neurol.*, 13, 1, 1991.
62. **Falsaperla, A., Monici-Preti, P. A., and Oliani, C.,** Selegiline versus oxiracetam in patients with Alzheimer-type dementia, *Clin. Ther.*, 12, 376, 1990.
63. **Ferrero, E.,** Controlled clinical trial of oxiracetam in the treatment of chronic cerebrovascular insufficiency in the elderly, *Curr. Ther. Res.*, 36, 298, 1984.
64. **Parnetti, L., Mecocci, P., Petrini, A., Longo, A., Buccolieri, A., and Senin, U.,** Neuropsychological results of long-term therapy with oxiracetam in patients with dementia of Alzheimer type and multi-infarct dementia in comparison with a control group, *Neuropsychobiology*, 22, 97, 1989.
65. **Foltyn, P., Lucker, P. W., Schnitker, J., and Wetzelsberger, N.,** A test model for cerebrally active drugs as demonstrated by the example of the new substance aniracetam, *Arzneim-Forsch/Drug Res.*, 33, 865, 1983.
66. **Macchione, C., Molaschi, F., Fabris, F., and Feruglio, F. S.,** Results with piracetam in the management of senile psycho-organic syndromes, *Acta Ther.*, 2, 261, 1976.
67. **Parnetti, L., Bartorelli, L., Bonaiuto, S., Cucinotta, D., Cuzzupoli, M., Erminio, F., Maggioni, M., Marini, G., Paciaroni, E., Pedrazzi, F., Peruzza, M., and Senin, U.,** Aniracetam (Ro 13-5057) for the treatment of senile dementia of Alzheimer type: results of a multicentre clinical study, *Dementia*, 2, 262, 1991.
68. **Green, R. C., Goldstein, F. C., Auchus, A. P., Presley, R., Clark, S., Van Tuyl, L., Green, J., Hersch, S. M., and Karp, H. R.,** Treatment trial of oxiracetam in Alzheimer's disease, *Arch. Neurol.*, 49, 1135, 1992.
69. **Davies, P. and Maloney, A. J. F.,** Selective loss of central cholinergic neurons in alzheimer's disease, *Lancet*, 2, 1403, 1976.
70. **Summers, W. K., Majowski, V., Marsh, G. M., Tachiki, K., and Kling, A.,** Oral tetrahydroaminoacridine in long term treatment of senile dementia, Alzheimer Type, *N. Engl. J. Med.*, 315, 1241, 1986.
71. **Davies, B., Andrewes, D., Stargatt, R., Ames, D., Tuckwell, V., and Davis, S.,** Tacrine in Alzheimer's disease, *Lancet*, July 15th, 1989.
72. **Chatellier, G. and Lacomblez, L.,** Tacrine (tetrahydroaminoacridine; THA) and lecithin in senile dementia of the Alzheimer type: a multicenter trial, *Br. Med. J.*, 300, 495, 1990.
73. **Gauthier, S., Bouchard, R., Lamontagne, A., Bailey, P., Bergman, H., Ratner, J., Tesfaye, Y., St-Martin, M., Bacher, Y., Carrier, L., Charbonneau, R., Clarfield, M., Collier, B., Dastoor, D., Gauthier, L., Germain, M., Kissel, C., Krieger, M., Kushnir, S., Masson, H., Morin, J., Nair, V., Neirinck, L., and Suissa, S.,** Tetrahydroaminoacridine-lecithin combination treatment in patients with intermediate-stage Alzheimer's disease, *N. Engl. J. Med.*, 322, 1272, 1990.
74. **Molloy, D. W., Guyatt, G. H., Wilson, D. B., Duke, R., Rees, L., and Singer, J.,** Effect of tetrahydroaminoacridine on cognition, function and behaviour in Alzheimer's disease, *Can. Med. Assoc. J.*, 144, 29, 1991.
75. **Davis, K. L., Thal, L. J., Gamzu, E. R., Davis, C. S., Woolson, R. F., Gracon, S. I., Drachman, D. A., Schneider, L. S., Whitehouse, P. J., Hoower, T. M., Morris, J. C., Kawas, C. H., Knopman, D. S., Earl,**

N. L., Kumar, V., Doody, R. S., Tacrine Collaborative Study Group. A double-blind, placebo-controlled multicenter study of tacrine for Alzheimer's disease. *N. Engl. J. Med.*, 327, 1253, 1992.

76. **Farlow, M., Gracon, S. I., Hershey, L. A., Lewis, K. W., Sadowsky, C. H., and Dolan-Ureno, J.,** A controlled trial of tacrine in Alzheimer's disease, *JAMA*, 268, 2523, 1992.
77. **Eagger, S., Morant, N., Levy, R., Sahakian, B.,** Tacrine in Alzheimer's Disease. Time course of changes in cognitive function and practice effects, *Br. J. Psychiatry*, 160, 36, 1992.
78. **Knapp, M., Knopman, D. S., Solomon, P. R., Pendlebury, W. W., Davis, C. S., and Gracon, S. I.,** A 30-week randomized controlled trial of high-dose tacrine in patients with Alzheimer's disease, *JAMA*, 271, 991, 1994.
79. **Maltby, N., Broe, G. A., Creasey, H., Jorm, A. F., Christensen, H., and Brooks, W. S.,** Efficacy of tacrine and lecithin in mild to moderate Alzheimer's disease: double blind trial, *Br. Med. J.*, 308, 879, 1994.
80. **Wilcock, G. K., Surmon, D. J., Scott, M., Boyle, M., Mulligan, K., Neubauer, K. A., O'Neill, D., and Royston, V. H.,** An evaluation of the efficacy and safety of tetrahydroaminoacridine (THA) without lecithin in the treatment of Alzheimer's disease. *Age and Ageing*, 22, 316, 1993.
81. **Wood, P. C. and Castleden, C. M.,** A double-blind, placebo-controlled, multicentre study of tacrine for Alzheimer's disease, *Int. J. Geriatr. Psychiatry*, 9/8, 649, 1994.
82. **Gustafson, L.,** Physostigmine and tetrahydroaminoacridine treatment of Alzheimer's disease, *Acta Neurol. Scand.*, 149 (Suppl.), 39, 1993.
83. **Debert, W.,** Interaction between psychological and pharmacological treatment in cognitive impairment, *Life Sci.*, 55, 2057, 1994.
84. **Locke, K. W., Gorney, B., Cornfeldt, M., and Fielding, S.,** Characterization of the discriminative stimulus effects of physostigmine in the rat, *J. Pharmacol. Exp. Ther.*, 250, 241, 1989.
85. **Martignoni, E., Petraglia, F., Costa, A., Bono, G., Genazzini, A. R., and Nappi, G.,** Dementia of the Alzheimer type and hypothalamus pituitary-adrenocortical axis: changes in cerebrospinal fluid, corticotropin releasing factor, and plasma cortisol levels, *Acta Neurol. Scand.*, 81, 452, 1990.

al Journal of Psychophysiology, 4 (1986) 41–52
Elsevier

ALUATION OF THE EFFICACY OF PIRACETAM IN TREATING INFORMATION ROCESSING, READING AND WRITING DISORDERS IN DYSLEXIC CHILDREN

ULA TALLAL[1], CHRISTOPHER CHASE, GUY RUSSELL and R. LARRY SCHMITT

niversity of California, San Diego, La Jolla, California and [2] Children's Hospital and Health Center, San Diego, CA (U.S.A.)

cepted September 30th, 1985)

words Piracetam – dyslexia – information processing – children

Piracetam, a new class of drug (nootropil) thought to enhance specific cognitive skills, was given in a 3300 mg daily dose to half of roup of fifty-five dyslexic boys aged 8–13 years, in a 12-week, double-blind, placebo-controlled study. The other half of the subjects eived placebo. All subjects met the following criteria: normal intelligence, normal educational opportunities, no severe emotional oblems, no neurological handicaps, good physical health, not taking other psychotropic medication, and scoring at least one and one f years below their mental age equivalent on the Gilmore Oral Reading Test. Non-verbal (auditory and visual) and verbal ce and memory skills were examined, and reading, spelling, language and writing abilities were measured using standardized tr. Compared to the placebo control group, individuals treated with Piracetam did not show statistically significant provements above their baseline scores on measures of perception, memory, language, reading accuracy or comprehension, or ting accuracy. However, reading speed and numbers of words written in a timed period were significantly enhanced in subjects ated with Piracetam as compared to placebo. Effective reading and writing ability, taking both rate and accuracy into sideration, were also significantly improved in the Piracetam as compared to the placebo treatment group. The medication was l-tolerated and medical examinations showed no significant adverse reactions. These results encourage further study of Piracetam determine more precisely the mechanism of action by which specific cognitive skills are affected.

TRODUCTION

Recent reviews of chemotherapeutic treatment learning disabilities have emphasized that the rceptual and behavioral changes induced by ugs do not necessarily lead to improved academic rformance (Aman, 1980; Werry, 1981). This nclusion has been based primarily on research th central nervous system stimulants such as ethylphenidate (Ritalin) and dextroamphetamine exedrine). Such stimulants have been shown to prove attention span (Barkley, 1977; Barkley d Jackson, 1977), memory (Sprague, 1972; Werry and Aman, 1975), and impulsivity and social behavior (Barkley and Cunningham, 1980; Conners and Werry, 1979). However, studies of educational abilities using standardized reading, spelling and arithmetic tests have failed to demonstrate any significant differences in the performance of treated children (Quinn and Rapoport, 1975; Weiss et al., 1975) or non-hyperactive children (Gittleman-Klein and Klein, 1976; Aman and Werry, 1982).

This discrepancy between the drug-induced improvements in behavioral control and the absence of change in school-performance may be due in part to the way each child is assigned the proper dosage. In the past, clinicians and investigators have assumed that the optimal dosage to improve

rrespondence: P. Tallal, Department of Psychiatry M-030p, iversity of California, San Diego, La Jolla, California, U.S.A.

behavior would coincide with the levels of drug needed for improved learning. Gittleman-Klein and Klein (1975) demonstrated, however, that there was no association between improvements in behavior and increases on academic test scores among children treated with Ritalin. Sprague and Sleator (1977) have proposed an inverted U-shaped functional relationship between the medication dosage and performance on cognitive or behavioral tasks. There is a zone of peak-enhancement or actual deterioration of the performance. Their studies have suggested that zones of peak-enhancement are not the same for cognitive and behavioral tasks. The optimal zone for social tasks requires a slightly higher dosage than the optimal zone for cognitive tasks. Thus, the best dosage for cognitive tasks appears to be too low to enhance social functioning, whereas the optimal zone for social enhancement is too high a dosage for improving cognitive skills. Since stimulants are usually prescribed for improving social behavior, children taking these medications may be receiving dosages that are too high for enhancing cognitive skills.

To avoid the ambiguities of such dosage-dependent effects, many investigators have focused their efforts on the study of cognitive effects due to psychotropic medications. Recent attention has been given to a new class of psychoactive drugs called nootropils. Piracetam, a nootropic substance, has been studied for its facilitation of learning and memory consolidation (UCB, 1980). Chemically, Piracetam (2-oxo-pyrrolidine-acetamide) shows a kinship to γ-aminobutyric acid GABA and appears to have no stimulating or sedating effects (Stegink, 1972; Calliauw and Marchau, 1975). Dimond (1975) and Dimond and Brouwers (1976) report that Piracetam increased verbal learning and improved performance on coding and short-term memory tasks with normal adult subjects. Other researchers have also noted that Piracetam significantly enhances performance on a variety of tasks which assessed presumed left-hemispheric functioning (Squitieri et al., 1975; Mindus et al., 1976). As such, Piracetam may be a particularly appropriate drug for treating children with some forms of learning disabilities including dyslexia, since many such children have been shown to have relatively poor perceptual and short-term memory abilities (Rudel and Denckla, 1974; Tallal, 1980a; Tallal, 1980b) and poor coding and naming abilities (Symmes and Rapoport, 1972; Denckla and Rudel, 1976).

Three studies have tested the effects of Piracetam on learning-disabled populations. The first study reported was by Wilsher et al. (1979), who used adult dyslexics as subjects. In this study, 16 adult dyslexics were matched on the basis of their WAIS IQ scores with 14 control subjects for a 3-week placebo-controlled, double-blind, crossover trial of 4800 mg daily dose of Piracetam. The dyslexic subjects met the criteria outlined by Thomson (1977). Since subjects in this study demonstrated significant carryover effects due to the crossover design, Wilsher et al. only examined results from the first period of treatment to avoid the confounding effects from previous exposure to Piracetam. In comparison to placebo treatment, results showed that in the dyslexic group who received Piracetam verbal learning improved by almost twice that of the non-dyslexic control group receiving Piracetam (15% compared to 8.6%). The test used was a serial memory verbal learning task with 10 three-letter nonsense syllables. In addition, the number of instances that a subject learned the nonsense syllable and then forgot it on the very next trial dropped by almost half among the dyslexic group treated with Piracetam (−47.1%), but was not changed in the dyslexic placebo treatment group.

Simeon et al. (1980) were the first to test the efficacy of Piracetam on learning skills of children. They treated 29 'learning disordered' boys between the ages of 8 and 14 with a 4800 mg daily dose of Piracetam in a double-blind, crossover placebo-controlled 4-week study. All children were at least one year behind their age group in either reading, spelling or arithmetic on the Wide Range Achievement Test (WRAT) and all had a Full Scale WISC-R IQ of at least 85. Their findings on measures of global behavior and learning were non-significant, although the author points out that the short duration of treatment, carryover effects due to the crossover design, and the small number of patients in various treatment subgroups made statistical analyses difficult to interpret.

In a second study by Wilsher et al. (1985), 46

dyslexic boys aged 8 to 13 years were treated in an 8-week, double-blind, placebo-controlled trial of 3300 mg daily of Piracetam. All subjects met the following criteria: they had a Full Scale WISC-R IQ greater than 90, a Reading or Spelling Age of at least two years behind their mental age based on the WISC-R, normal educational opportunities, no severe emotional problems, normal hearing and normal vision, and no gross neurological deficits. The children were tested on their reading ability (speed, accuracy, and comprehension) and a 5-min free-writing sample was taken to measure the total number of words written and the percentage of spelling mistakes. *T*-test comparisons between the means of the two treatment groups at the beginning and the end of the 8 weeks showed no significant differences on any of the dependent measures. However, further analysis comparing the mean treatment changes from baseline, using the difference between the post- and pretreatment scores for each subject, revealed improvements in reading speed and accuracy and total words written by individuals treated with Piracetam. In all 3 studies, the Piracetam medication was extremely well-tolerated.

The present study was designed to replicate and extend the findings of Wilsher et al. (1984). More rigorous patient-selection inclusion and exclusionary criteria were used. Drug dosage and regimen were equivalent, but the clinical trial was extended to 12 weeks and additional subjects, test sites, and psychometric tests were included.

METHODS

Subjects

Six different centers participated in the study. At our site in San Diego, 61 developmentally reading-disabled children were studied over a one and a half year-period, from the spring of 1981 to the summer of 1982. All children attended school during the course of the study and met the following criteria. (1) They were male and between the ages of 8 years, 0 months and 13 years, 11 months old at the initial visits. (2) They had a Full Scale IQ score of 80 or more on the Wechsler Intelligence Scale for Children-Revised (WISC-R) with a Performance Scale IQ or a Verbal Scale IQ of 90 or more, obtained within 9 months of the initial visit. (3) They had a Reading Quotient of less than or equal to 0.85. (4) English was their primary language. (5) Informed consent was obtained from both patient and parent or legal guardian. (6) They had normal audiological and ophthalmological functioning. (7) There was no significant neurological handicap. (8) They had no severe emotional disturbance as a primary symptom. (9) There was no severe educational deprivation. (10) They had no clinically significant laboratory abnormalities, nor any medical conditions which might put the patient at additional risk or interfere with the conduct of the study. (11) They had no history of significant adverse reaction or hypersensitivity to Piracetam. (12) They were not involved in any therapies which might interfere with the evaluation of efficacy and safety, including: psychostimulant medication within 6 months of the initial visit, concomitant drug therapy with psychostimulants or any drug for emotional disturbance, concomitant therapy with Tofranil for any indication, investigational drug therapy within one month of the initial visit, or concomitant chronic treatment with bronchodilators which have central stimulant activity.

The Reading Quotient was calculated as equal to: Reading Age × 100% by Chronological Age × Full Scale WISC-R IQ. The Reading Age was derived from the Accuracy Score of the Gilmore Oral Reading Test — Form C. Grade Scores from the Gilmore were converted to Age Scores using Table II provided in the Gates-McKillop Oral Reading Test. Abnormal audiological functioning was defined as a loss of greater than 20 dB in either ear for two frequencies in the normal range (500, 1000, 2000, 3000, 4000 Hz, using pure tones). Abnormal ophthalmological functioning was defined as less than 20/40 corrected vision in both eyes as tested by the American Optical E Chart. Significant neurological handicaps were defined as any of the following: acquired neurological disease, classical neurological signs with functional impairment or seizures within the last 5 years. The patients had not received anticonvulsant therapy for at least two years prior to the initial visit. Educational and emotional evaluations were made

by the medical staff following usual clinical practice. Four subjects were dropped from the study: one moved, one suffered from an asthma attack and was treated with bronchodilators (in violation with the protocol) and two were removed from the study due to medical complications unrelated to study medication (both were taking placebo). The fact that a child was currently receiving academic remedial assistance or had received such tutoring in the past did not preclude entry into the study.

Procedures

Placebo and Piracetam treatments were randomly divided among 6 groups of 10 subjects, each on a double-blind basis with the restriction that there be equal numbers of each treatment within each of the 6 groups. Patients were then assigned to one of the 6 groups on the basis of their age; that is, 8-year-olds were assigned to Group One, 9 years olds to Group Two, and so forth. When all the treatment medication had been used up within a group, the patient was assigned to the group with the fewest members. Patients received either 3.3 g of Piracetam daily or matching placebo syrup. Each dose of test medication was 5 ml, administered before breakfast and again before the evening meal. A 5 ml dose of active medication contained 1.65 g of Piracetam. No dosage adjustments were allowed.

The study consisted of 5 visits. An initial screening visit usually occurred one week prior to the start of treatment. The treatment period was 12 weeks long, with follow-up visits after 2 weeks, 6 weeks, and 12 weeks of treatment. At week 4 and week 9, the patient's parents were contacted to review dosage instructions and to determine whether any adverse effects had been observed.

At the initial screening, patients were tested to determine their eligibility. Hearing and visual acuity tests were given, a developmental history taken, IQ testing was done as needed, and the Gilmore Oral Reading Test was also administered to provide a calculation of the Reading Quotient. Assessment of education experience and emotional health was also performed at this time.

A complete physical examination was performed by a physician at the second or induction visit and again at the last visit. A medical history was taken during the second visit and abbreviated physical examinations were performed at the second and sixth week visits. Observations for possible adverse effects and assessment of general health were emphasized. Laboratory evaluations were obtained at the induction visit, the 6-week, and the 12-week visits. The laboratory tests included hematology, urinalysis and blood chemistry to test for possible adverse side-effects.

Tests

All 6 study centers followed the same protocol and used a common battery of tests to measure drug efficacy. In addition, each site conducted additional 'special studies'. Only the results from the common test battery and special study conducted at the San Diego site are reported in this paper. The common test battery was administered at the induction and final (week 12) visits, while the special study tests were given at the induction and week 6 visit. At the San Diego Center, all testing for an individual patient was administered by the same tester and took approximately $1\frac{1}{2}$ h. These tests included: the Gilmore Oral Reading Test — Form C at the initial visit and Form D at the final visit —, Information for Reading Accuracy, Comprehension and Rate were included; the Digit Span subtest of the WISC-R, both digits forwards and backwards administered via a tape recording; the Gates-McKillop Syllabication subtest — Form 1 at the induction and Form 2 at the 12-week visit; the Wide Range Achievement subtest for Spelling; a 5-min free-writing sample was taken to include the total number of words, number of words misspelled and the number of occurrences of the most frequently written word; the Rapid Automatized Naming Test (Denckla and Rudel, 1976); a behavioral assessment in the testing situation made at the induction and 12-week visits on a rating scale of 1 to 4 (1 being excellent, 4 being poor), measuring distractibility from following instructions, social appropriateness, cooperativeness, attention and general motor activity; and a parent's global assessment of the child's behavior obtained at the 12-week visit on a rating scale of 1–5, where 1 is much improved and 5 is much worse, considering their behavior at home, interaction with peers and school reports concern-

g behavior and performance in evaluating the ange from the start of the study.

In addition to these common tests, we con- cted additional special studies. Subjects were en the Repetition Test, developed by Tallal 980), with 3 sets of stimuli: (1) non-verbal audi- y tones (75 ms duration), differing in funda- ntal frequency; (2) non-verbal visual nonsense apes (75 ms duration); and (3) auditory stop- nsonant vowel syllables (ba/da) with 40 ms ration formant transitions. The Repetition Test s been shown to be a highly sensitive measure of ceptual and memory functioning. In addition, s theoretically based on a model of perception d is comprised of a series of substests designed assess levels of perception and memory in a rarchical manner (see Tallal, 1980, for a detailed scription of these procedures). Four dependent asures were made on each of the 3 versions of Repetition Test. Subjects were scored for the al number of correct trials, the number of cor- t trials using interstimulus intervals (ISI's) of) ne number of trials using ISI's less than) ms and the number of trials needed to reach terion. Improvements in trials to criterion scored licate an increased rate of learning stimulus–re- nse associations. Increases in scores on trials h short ISI's suggest an improvement in rate of cessing and temporal sequencing abilities. provements in the longer ISI scores suggest an rease in short-term and serial memory.

In addition to these experimental perceptual d memory tests, subjects were also given the ken Test (DeRenzi and Vignolo, 1962) to assess eptive language comprehension skills and a red associate visual memory test designed for s study. In the visual memory test the tester tructed the child by saying, 'I would like to see w well you can remember different pairs of tures. I will show you two pictures, one after other. Try to remember them as a pair that go ether'. Testing took place in two parts, a learn- and a recall section. During the learning sec- n, children were presented with pairs of pictures anged as a set. Children were presented with s of 2, 4, 6 and then 8 pairs. If a child success- y recalled all pairs within a set, they moved to e higher set and were tested. If any failure occurred, the final testing took place using the next lowest set; e.g., failure on set 6, final testing on set 5. During the learning portion, children were presented with pairs of pictures, one after the other, until the set was completed. Each pair was presented for 3 s with an intertrial interval of two seconds. After all of the pictures in a set had been presented, the child's recall abilities were tested in the following way: the second picture of each pair was grouped, mixed and then laid down on the table in front of the child. Using the same order as presented in the learning portion of the test, the first picture of each pair was presented to the child, and he was asked to find the picture that goes with it among the pictures laid down on the table in front of him. This procedure was continued until all pictures had been matched. Children were scrored for the total number of correctly matched pictures. Improvements on this test suggest increases in visual learning and recall.

RESULTS

From the initial sample of 61 children, 57 successfully completed the study. From this group, two children had poor compliance during the last 6 weeks of the clincial trial period (below 70% as measured from the remaining bottled medication). Consequently, they were removed from the data analysis leaving 55 children, 28 from the piracetam treatment group and 27 in the placebo treatment group.

Table I presents the demographic and baseline characteristics of the Piracetam and placebo treatment groups. *T*-test and χ^2 comparisons between the two groups showed no significant demographic differences. Note that a high percentage of the children were actively receiving remedial tutoring for their reading problems (ca. 70%).

Table II shows the baseline scores for the Piracetam- and placebo-treated groups on the common test battery. Note that the Gilmore Oral Reading test was scored in two ways. First, individual reading ability for accuracy, comprehension and rate was scored. Second, because by reading more slowly, accuracy and comprehension may be improved or vice versa, composite reading scores

TABLE I

Demographic and baseline characteristics

Patient characteristic	*Piracetam (n = 28)*	*Placebo (n = 27)*	*P*
Age, years			
Mean	11.1	11.4	$t = -0.05$ n.s.
S.D.	1.9	1.6	
WISC-R, VSIQ			
Mean	97.8	98.0	$t = -0.1$ n.s.
S.D.	10.9	10.8	
WISC-R, PSIQ			
Mean	107.2	107.1	$t = 1.0$ n.s.
S.D.	11.2	12.1	
WISC-R, FSIQ			
Mean	102.4	102.5	$t = -0.1$ n.s.
S.D.	9.6	11.2	
Reading quotient			
Mean	0.73	0.72	$t = 0.9$ n.s.
S.D.	0.07	0.07	
Reading class			
Tutoring	20	20	$\chi^2 = 0.0$ n.s.
No tutoring	8	7	
Relatives			
Dyslexic	18	21	$\chi^2 = 0.5$ n.s.
Non-dyslexic	10	6	

n.s. = not significant, $P > 0.05$.

were calculated to reflect the interaction between reading speed, and reading accuracy and comprehension. A composite score for 'effective reading accuracy' was calculated by multiplying the percentage of words read correctly by the reading rate. Similarly, 'effective reading comprehension' scores were calculated by multiplying the percentage of correctly answered comprehension questions by the reading rate (Jackson, 1980). Scores are multiplied rather than added together, because they use different units of measurement. Composite reading scores are always a positive number and reflect a child's total reading effort.

T-test comparisons between groups at baseline showed non-significant difference on all but one measure. The placebo group performed significantly better than the Piracetam group at baseline on the percentage of spelling errors in the free-writing test ($t = 2.64$, $P < 0.01$). There were no other significant baseline differences between groups on the common test battery.

Table III gives the baseline scores for the Piracetam- and placebo-treated groups on the experimental test battery. *T*-test comparisons between groups at baseline again showed no significant difference on all but one measure. The placebo group performed significantly better than the Piracetam group on the Paired Associate Visual Memory Test at baseline ($t = 2.0$, $P < 0.05$). There were no other baseline differences on the experimental test battery.

To assess the effect of drug treatment, the mean change from baseline was calculated for each subject on each measure and then averaged and compared for each treatment group.

Table IV shows the mean change from baseline (posttest–pretest scores) for each measure in the common test battery for the Piracetam and placebo groups. As seen in Fig. 1 for individual reading scores, the Piracetam group demonstrated a statistically significant improvement over the placebo group (at the $P < 0.003$ level of accuracy) on their reading rate from the Gilmore test. The Piracetam group increased their reading speed by almost 8 words per min (−10%) whereas the placebo group decreased by 3 words per min (−4%), leaving a difference of almost 11 words per min between the

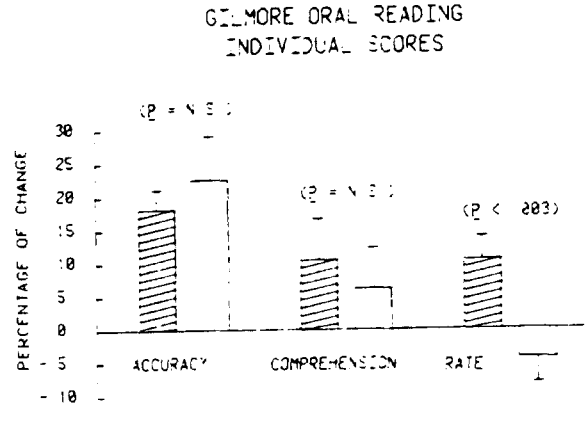


Fig. 1. Percentage of change from baseline (posttest minus pretest scores) made by the Piracetam and placebo treatment groups are shown for the accuracy, comprehension and rate scores of the Gilmore Oral Reading Test.

ABLE II

seline scores for the Piracetam and placebo groups on the common test battery

st name	*Piracetam*	*Placebo*	*t-test*
lmore oral reading			
Accuracy (grade rating)	3.3	3.1	n.s.
Reading comprehension (grade rating)	4.8	4.9	n.s.
ading rate (words min)	76.9	77.6	n.s.
lmore composite reading (% correct × rate)			
Accuracy	6 774.3	6 883.9	n.s.
Comprehension	6 646.3	6 683.3	n.s.
git span (scaled score)	7.2	7.2	n.s.
ites-McKillop syllabication raw score)	11.6	12.1	n.s.
ords written (total)	41.0	44.1	n.s.
rcent of spelling errors [b]	21.5	12.3	$P < 0.01$ [a]
in color [b]	42.3	46.7	n.s.
in number [b]	31.4	35.0	n.s.
in l[illegible] [b]	32.4	37.1	n.s.
in c[illegible] [b]	61.3	65.0	n.s.

ne-tailed test of significance; [b] reduction in score indicates improvement.

ABLE III

seline scores for the Piracetam and placebo groups on the perimental test battery

st name	*Piracetam*	*Placebo*	*t-test*
on-verbal — ual test			
Long ISI's	23.4	23.4	n.s.
Short ISI's	10.9	11.5	n.s.
petition test — lables			
Long ISI's	13.5	12.7	n.s.
Short ISI's	7.1	6.8	n.s.
petition test — n-verbal auditory			
Long ISI's	19.2	21.4	n.s.
Short ISI's	11.3	13.1	n.s.
ired associate Memory test	18.9	24.5	$P < 0.05$ [a]
iken test			
Parts 1–4	8.6	8.6	n.s.
Pa[illegible]	17.7	18.2	n.s.

[a] One-tailed test of significance.

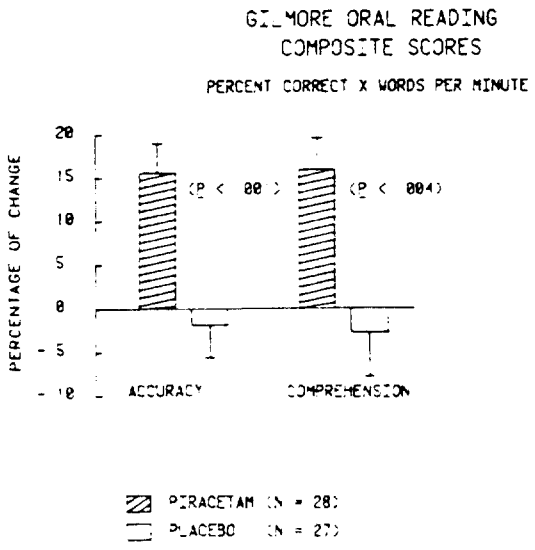


Fig. 2. The Composite Reading scores, derived by multiplying the percentage correct by the number of words read per min, on the Gilmore Oral Reading test are shown for the Piracetam and placebo treatment groups. Percentage change from baseline (posttest minus pretest composite scores) are shown separately for accuracy and comprehension.

TABLE IV

Mean change from baseline score for the Piracetam and placebo groups on the common test battery

Test name	*Mean change from base-line (post- pretest score)*				
	Piracetam	*Placebo*	*t*	*d.f.*	*P* [a]
Gilmore oral reading					
Accuracy (grade rating)	0.6	0.7	−0.55	53	0.29
Reading comprehension (grade rating)	0.5	0.3	0.40	53	0.34
Reading rate (words/min)	8.0	−3.4	2.39	53	0.003
Gilmore composite reading (% correct × rate)					
Accuracy	1055.6	−132.1	3.43	53	0.001
Comprehension	1054.0	−189.7	2.98	53	0.003
Digit span (scaled score)	0.9	0.3	1.03	53	0.15
Gates-McKillop syllabication (raw score)	2.2	2.9	−0.83	53	0.21
Wrat spelling (grade rating)	0.2	0.3	−0.49	53	0.31
Words written (total)	6.1	2.2	1.08	51	0.14
Percent of spelling errors [b]	−4.1	7.4	−2.51	51	0.008
Ran color [b]	−1.9	−1.3	−0.30	53	0.38
Ran number [b]	−1.6	−2.5	0.70	53	0.24
Ran letter [b]	−2.1	−3.1	0.55	53	0.29
Ran object [b]	−3.4	−1.3	−0.73	53	0.24

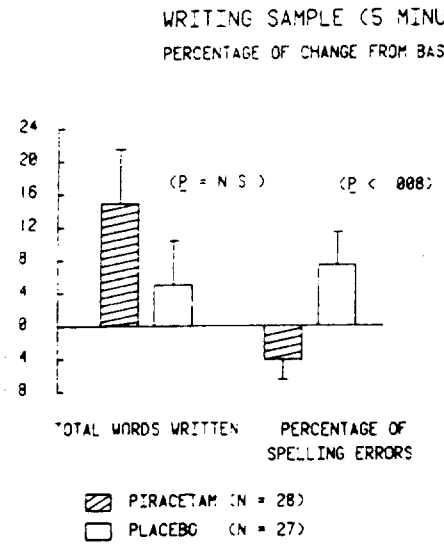
[a] A one-tailed test of significance; [b] reduction in score indicates improvement.

two groups. This increase in reading speed for the Piracetam group was accompanied by improved reading accuracy and comprehension, although similar gains were also found in the placebo group and, thus, cannot be ascribed to drug effect. There were no significant differences between groups on reading accuracy or comprehension.

Composite reading test scores shown in Fig. 2 demonstrate that the Piracetam group significantly improved their effective reading by 16% during the course of the study, on both their effective reading accuracy and comprehension scores, whereas the placebo group decreased on both composite reading scores. This difference in performance between the two treatment groups was highly significant (effective reading accuracy, $t = 3.43$, $P < 0.001$; effective reading comprehension, $t = 2.98$, $P < 0.004$).

A comparison of composite and individual reading scores reveals that although the placebo group did increase in their reading accuracy and comprehension this was accomplished at the expense of their reading speed which decreased, producing very little effective change in their overall reading performance. The Piracetam group, on the other hand, not only improved their reading accuracy and comprehension but also simultaneously was able to increase their reading rate. This resulted in significant gains in their overall reading performance.

Fig. 3 shows that on the Free-Writing Test, both groups showed an increase in the total number of words written. The Piracetam group improved 15% whereas the placebo group showed only a 5% gain, although this difference was not statistically significant. The Piracetam group, how-



3. Percentage of change from baseline (posttest minus test scores) made by the Piracetam and placebo treatment ups are shown for the 5-min free-writing sample. The total nber of words written in 5 min by each treatment group, as l as the percentage of spelling errors are graphed.

er, show significant improvement over the acebo group in the accuracy of their spelling < 0.008). The Piracetam group decreased the rcentage of spelling errors (number of errors/ al words written) by 4% whereas the placebo oup increased in spelling errors by over 7%. ese figures change, however, if one placebo 'out-r' subject, who scored well above the rest of the oup (83%), is removed from the analysis. Then e placebo group shows only a 4.5% increase in elling errors ($P < 0.02$). Nevertheless, the trends nain the same. Overall, the Piracetam group not ly increased in their writing speed, but also proved in their spelling accuracy. The placebo oup's increase in writing speed, however, was set by additional spelling errors.

Analysis of the mean change from baseline retest–posttest scores) for each measure in the perimental test battery for the Piracetam and acebo groups showed that there were no signifi-nt differences found between treatment groups any of the experimental perceptual, memory or nguage measures given.

Results from laboratory evaluations of blood emistry, hematology and urinalysis were consistent with previous findings, showing no significant medical abnormalities among the Piracetam-treated subjects. The double-blind rating of drug tolerance by the physician indicated that Piracetam was well-tolerated by the children (mean rating = 1.1 ± 0.1), 1 excellent, 4 poor). Except for the one child who suffered from an asthma attack, all the children who were treated with Piracetam remained healthy.

DISCUSSION

These results confirm some of the previous findings of Wilsher et al. (1984) that Piracetam increases the rate of reading and of writing accuracy. The amount of changes found in this present study are comparable to the results obtained by Wilsher. In Wilsher's 8-week study, subjects improved their reading rate by 5%. The amount of change found in the present 12-week study is proportional to Wilsher's data with a 10% improvement in reading rate. This finding, seen in the light of Wilsher's previous data, suggests that the degree of Piracetam-induced improvement in reading and writing may be related to the duration of treatment. However, improvement over time was not assessed directly in the present study. Additional studies will be necessary to establish the effects of dose-duration.

The present study failed to confirm Wilsher's previous findings of drug-improved reading accuracy. The lack of improvement may be due in part to some very large placebo responders; in fact, the largest improvement in reading accuracy (79%) was found in a member of the placebo group.

Substantial changes in reading accuracy and comprehension ability occurred over the course of the study for many of the dyslexic children in both the Piracetam- and placebo-treated groups. This was somewhat unexpected as the reading skills of dyslexic children as a group are known to be difficult to remediate. These marked changes in reading suggest that perhaps the attention and positive reinforcement given to the children in the study, together with the expressed goal of helping them improve their reading skill by using a unique method, a medication, added to the improvement

made. It is of considerable interest that the improvements noted in the placebo-treated group mirror the instructions given to them on reading and writing tests.

On the Gilmore reading test children were told to read the passages as well as they could. Although the children on placebo did improve their reading accuracy and comprehension, as instructed to do, they did so by slowing down their rate of reading (over their baseline reading rate) to achieve this improvement. Thus, they had to lose ground in rate in order to gain it in accuracy and comprehension. The dyslexics on Piracetam, on the other hand, did not need to resort to this strategy to achieve improvement in reading accuracy and comprehension. Rather, they were able to significantly increase their reading rate as well as their accuracy and comprehension over their original baseline performance. That is, they did not have to lose ground in order to gain ground. They gained both speed and improved accuracy and comprehension over the course of the study. The percentages of subjects in the Piracetam and placebo treatment groups showing gains and losses in reading accuracy and rate are shown in Fig. 4.

On the writing sample subjects were told to write as much as they could during a specified time-period. The placebo-treated children did just that. They increased the number of words written over their original baseline performance. However, as was found in reading, they made this gain at the expense of something else, in this case an increased number of spelling errors. The dyslexics on Piracetam did not show this 'lose-to-gain' pattern. Rather, they increased both the number of words written as well as decreasing the number of spelling errors they made. Even though the only significant difference between groups noted at baseline was the number of spelling errors made, with the Piracetam group making more errors than the placebo group, by the end of the study this order was reversed. The Piracetam group made fewer spelling errors than the placebo group.

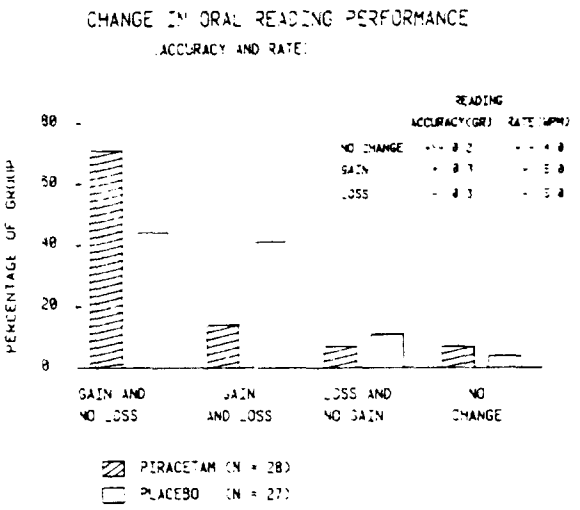


Fig. 4. Composite reading scores, derived by multiplying reading accuracy by rate (words read per min), on the Gilmore Oral Reading test are graphed to show the percentage of the Piracetam and placebo treatment group who made gains and losses in effective reading ability over the course of the study.

Some of the measures in the special perceptual, memory and receptive language studies suffered from ceiling effects, as most of the subjects found these tests to be relatively easy, indicating adequate perceptual, memory and language abilities for their age. Most of the subjects performed at the top of the scale on all subtests of the Repetition Test as well as on all 5 parts of the Token Test, indicating normal perception and receptive language abilities at the onset of the study, hence leaving little room for improvement. Only 4 subjects scored at least one standard deviation below the mean on the Token Test, suggesting that Mattis et al.'s (1975) language disorder syndrome was poorly represented in this dyslexic sample. Subjects also scored highly on perceptual subtests of all 3 Repetition Tests, indicating that they had no difficulty in discriminating between the different auditory or visual stimuli. A subgroup of 19 subjects did have difficulty discriminating between the two computer-synthesized speech syllables /ba/ and /da/ with 40 ms formant transitions. On the Repetition Test however, perhaps due to the very small sample size, a χ^2-test indicated no significant differences between Piracetam and placebo groups on this test. Contrary to previous findings (Dimond, 1975; Wilsher et al., 1979), subjects taking Piracetam did not demonstrate statistically significant improvements in their short-term and serial memory skills, although some differences between non-verbal and verbal stimuli were found.

sing non-verbal stimuli, treatment groups showed) significant differences on the total number of rrect stimulus series recalled in the auditory odality of the Repetition Test. In the visual odality, subjects on placebo found it easier to call the proper sequence of the visual nonsense-aped stimuli, as demonstrated by their improved ores for total correct trials with long ISI's. In ntrast, when test items could be verbally re-arsed, as in the Paired Associate Visual Memory est, which used namable pictures as stimuli, and ie Digit Span subtests, the Piracetam-treated oup's mean final performance and change from aseline was almost twice that of the placebo oup on both tests (Fig. 5). The difference be-een groups, however, was not statistically sig-ficant in either case. These trends toward im-roved memory for verbally mediated material ggest that a significant improvement in verbal emory scores might be realized with a larger mple size, a longer duration drug trial, or more nsitive measures. In addition, Piracetam's effect n memory could be mediated by drug-dosage. A ir[illegible].g. 4800 mg/day) dosage might produce gn..ant results, since previous findings used a osage in this range.

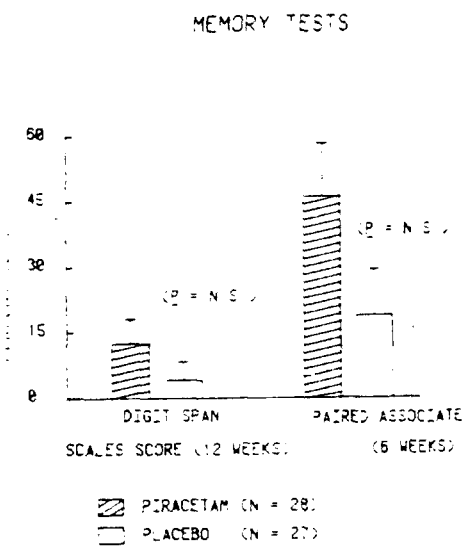


Fig. 5. The percentage of change from baseline (posttest minus pretest scores) made by the Piracetam and placebo treatment groups on two verbal memory tests, digit span and paired associate, are shown.

This pattern of results calls for a much closer examination of the different stages of memory that may be affected by Piracetam. Future studies should examine possible material-specific effects of Piracetam on various memory components, such as working capacity, rehearsal strategies, retrieval, retention and recall. In addition, the questions of dosage-dependent memory effects should be investigated.

Subject selection procedures may also have important implications for drug studies with dyslexic children. Several different subgroups of reading- or language-impaired children, exhibiting different profiles in the areas of perceptual, memory and language functions, have been described (see Tallal and Stark, 1982, for review). Baseline test scores suggest that the majority of reading-impaired children participating in this study did not have significant perceptual, memory or receptive language deficits associated with their reading disability. Thus, it was difficult to assess the potential therapeutic efficacy of Piracetam in treating such deficits in the present study. In order to better assess Piracetam's ability to effect perceptual, memory or receptive language deficits, it will be important to select a group of reading- or language-impaired children who show significant deficits in these areas at baseline testing. Comparisons between different subgroups of reading-impaired children, selected on the basis of specified behavioral profiles, may be an important factor in assessing the effects of nootropils on learning- and language-impaired children.

In summary, Piracetam appears to improve verbal fluency, as demonstrated by increased rates of reading and writing accuracy. These trends encourage a potential role for Piracetam in the clinical remediation of dyslexia, although questions about drug-dosage, duration of treatment, possible interaction with other remedial procedures, differential effects on various subgroups of learning-impaired children and selectivity of drug-response remain unanswered. Some of these issues are being investigated presently.

One final note of caution — given the number of analyses performed, some of the results obtained could be interpreted as chance occurrences. Selective replication of these findings with a differ-

ent group of dyslexic children is necessary to validate these results.

REFERENCES

Aman, M.G. (1980) Psychotropic drugs and learning problems — a selective review. *J. Learn. Disab.*, 13: 36–46.

Aman, M.G. and Weery, J.S. (1982) Methylphenidate and Diazepam and severe reading retardation. *J. Am. Acad. Child Psychiatry*, in press.

Barkely, R.A. (1977) The effects of Methylphenidate on various types of activity level and attention in hyperkinetic children. *J. Abnorm. Child Psychol.*, 5: 351–369.

Barkley, R.A. and Cunningham, C.E. (1980) The parent–child interactions of hyperactive children and their modification by stimulant drugs. In R.M. Knights and D.J. Bakker (Eds.), *Treatment of Hyperactive and Learning Disordered Children*. University Park Press, Baltimore.

Barkley, R.A. and Jackson, T.L. (1977) Hyperkinesis, autonomic nervous system activity and stimulant drug effects. *J. Child Psychol. Psychiatry*, 18: 347–357.

Calliauw, L. and Marchau, M. (1975) Clinical trial of Piracetam in disorders of consciousness due to head injury. *Acta Anaesthesiol. Belg.*, 26: 51–60.

Conners, C.K. and Werry, J.S. (1979) Pharmacotherapy. In H. Quay and J.S. Werry (Eds.), *Psychopathological Disorders of Childhood*. Wiley, New York.

Denckla, M.B. and Rudel, R.G. (1976) Rapid 'automatized' naming (R.A.N.): dyslexia differentiated from other learning disabilities. *Neuropsychologia*, 471–479.

De Renzi, E. and Vignolo, L.A. (1962) The Token Test: a sensitive test to detect receptive disturbances in aphasia. *Brain*, 85: 665–678.

Dimond, S.J. (1975) The effects of a nootropic substance on the capacity for verbal memory and learning in normal man. *Third Congress of International College of Psychosomatic Medicine*, 9: 16–20.

Dimond, S.J. and Brouwers, E.Y.M. (1976) Improvement of human memory through the use of drugs. *Psychopharmacology*, 49: 307–309.

Gittleman-Klein, R. and Klein, D.F. (1975) Are behavioral and psychometric changes related in methylphenidate-treated, hyperactive children? *Int. J. Ment. Health*, 4: 182–198.

Gittleman-Klein, R. and Klein, D.F. (1976) Methylphenidate effects in learning disabilities: psychometric changes. *Arch. Gen. Psychiatry*, 33: 655–669.

Jackson, M.D. (1980) Further evidence for a relationship between memory access and reading ability. *Journal of Verb. Learn. Verb. Behav.*, 19: 683–694.

Mattis, S., French, J.H. and Rapin, I. (1975) Dyslexia in children and young adults: three independent neuropsychological syndromes. *Dev. Med. Child Neurol.*, 17: 150–163.

Mindus, P., Cronholm, B., Levander, S.E. and Schalling, D. (1976) Piracetam-induced improvement of mental performance: a controlled study on normally aging individuals. *Acta Psychiat. Scand.*, 54: 150–160.

Quinn, P.O. and Rapoport, J.L. (1975) One year follow-up of hyperactive boys treated with Imipramine or Methylphenidate. *Am. J. Psychiatry*, 132: 241–245.

Rudel, R.G. and Denckla, M.B. (1974) Relation of forward and backward digit repetition to neurological impairment in children with learning disabilities. *Neuropsychologia*, 12: 109–118.

Simeon, J., Waters, B. and Resnick, M. (1980) Effects of Piracetam in children with learning disorders. *Psychopharmacol. Bull.*, 16: 65–66.

Sprague, R.L. (1972) Psychopharmacology and learning disorders. *J. Operat. Psychiatry*, 3: 56–67.

Sprague, R.L. and Sleator, E.K. (1977) Methylphenidate in hyperkinetic children: differences in dose effects on learning and social behavior. *Science*, 198: 1274–1276.

Squitieri, G., Cervone, A. and Agnoli, A. (1975) *A Study on Short-Term Memory in Man. Interactions with Noxanaleptic and Nootropic Drugs*. Paper presented at Third International College of Congress on Psychosomatic Medicine, Rome, Italy.

Steginк, K.J. (1972) The clinical use of Piracetam, a new nootropic drug: the treatment of senile involution. *Arzneim.-Forsch.*, 22: 975–977.

Symmes, J.S. and Rapoport, J.L. (1972) Unexpected reading failure. *Am. J. Orthopsychiatry*, 42: 82–91.

Tallal, P. (1980a) Perceptual requisites for language. In R. Schiefelbusch (Ed.), *Non-Speech Language and Communication*. University Park Press, Baltimore.

Tallal, P. (1980b) Auditory temporal perception, phonics and reading disabilities in children. *Brain Lang.*, 9: 182–198.

Tallal, P. and Stark, R.E. (1982) Perceptual/motor profiles of reading-impaired children with or without concomitant oral language deficits. *Anal. Dyslexia*, 32: 163–176.

Thomson, M.E. (1977) Identifying the dyslexic child. *Dyslexia Rev.*, 18: 5–12.

UCB (1980) *Nootropil*. UCB, Pharmaceutical Division, Brussels, Belgium.

Weiss, G., Kruger, E., Danielson, U. and Elman, M. (1975) Effect of long-term treatment of hyperactive children with methylphenidate. *Can. Med. Assoc. J.*, 11: 159–165.

Werry, J.S. (1981) Drugs and learning. *J. Child Psychol. Psychiatry*, 22: 283–290.

Werry, J.S. and Aman, M.G. (1975) Methylphenidate and Haloperidol in children: effects on attention, memory and activity. *Arch. Gen. Psychiatry*, 32: 790–795.

Wilsher, C., Atkins, G. and Mansfield, P. (1979) Piracetam as an aid to learning in dyslexia, preliminary report. *Psychopharmacology*, 65: 107–109.

Wilsher, C., Atkins, G. and Mansfield, P. (1985) Effects of Piracetam on dyslexics' reading ability. *J. Learn. Disabil.*, 18: 19–25.

The Effects of Nootropics on Memory: New Aspects for Basic Research

C. Mondadori, F. Petschke, A. Häusler
Pharmaceutical Research Department, CIBA-GEIGY Limited, Basle, Switzerland

Summary

The mechanism through which nootropics of the piracetam type (i.e., piracetam itself and its analogues oxiracetam, pramiracetam, and aniracetam) improve memory is still uncertain. Its elucidation will, however, not only mark an advance in the treatment of cognitive disorders, but also shed light on the basic processes of memory storage. Although the great majority of the findings available so far seem to suggest cholinergic mechanisms, divergent results are obtained whenever parallel experiments are performed with two or more of these compounds. More recent observations indicate that interactions with steroids take place. All four compounds are inactive in adrenalectomized laboratory animals; chemical blockade of the adrenal cortex with aminoglutethimide and pretreatment wich epoxymexrenon, a potent mineralocorticoid antagonist, eradicated the memory-enhancing effect of all four substances.

Wirkungen der Nootropika auf das Gedächtnis: Neue Aspekte für die Grundlagenforschung

Es besteht noch immer keine Gewißheit darüber, auf welche Weise die Nootropika des Piracetamtyps (Piracetam und dessen Analogverbindungen Oxiracetam, Pramiracetam und Aniracetam) das Gedächtnis verbessern. Die Klärung dieser Frage würde nicht nur einen Fortschritt bei der Behandlung kognitiver Störungen darstellen, sondern auch die der Gedächtnisspeicherung zugrundeliegenden Vorgänge erhellen. Obwohl die große Mehrzahl der bislang verfügbaren Befunde auf cholinergische Mechanismen hinweisen, werden widersprüchliche Ergebnisse erzielt, sobald parallele Experimente mit zwei oder mehreren dieser Verbindungen durchgeführt werden. Neuere Beobachtungen scheinen auf Wechselwirkungen mit Steroiden hinzudeuten: alle vier Verbindungen sind bei adrenalektomierten Labortieren unwirksam; sowohl eine chemische Blockierung der Nebennierenrinde durch Aminoglutethimid als auch eine Vorbehandlung mit Epoxymexrenon (einem potenten Mineralokortikoidantagonisten) blockierte die gedächtnisverbessernde Wirkung aller vier Substanzen.

The elucidation of biochemical bases and the regulation of memory is one of the greatest challenges in neurobiology. It is therefore hardly surprising that every year hundreds of papers are published dealing with some particular facet of memory. Our knowledge of the subject matter increases almost daily, but more in width than in depth. We now know of many transmitters, receptors, and modulators that play some part in memory processing; but each new finding is soon relativized by the realization that it is not generally valid, but simply sometimes true under certain limiting conditions. In this field, progress tends to follow the discovery of a new pharmacological tool, e.g., a new specific receptor blocker or activator, or an enzyme inhibitor. Consequently, the prevalent method in efforts to identify the mechanisms and the neuronal networks operative in memory processing relies on the testing of mechanistically specific preparations for potential effects on memory in animal models. For example, the NMDA blockers (MK 801, AP5, and AP7) that recently became available encouraged studies of the influence of NMDA blockade on learning and memory and speculation about the possible involvement of this type of receptor in memory processing (*Morris* et al., 1986). In the meantime, it has become evident that the responses seen under NMDA blockade only apply in certain circumstances and to certain processes of memory (*Mondadori* et al., 1989). Thus, while the assortment of transmitters involved in memory processing increases, that does nothing to alter the fact that almost every pharmacological manipulation of the CNS has some influence on certain, though not all, forms of learning and memory (*Mondadori*, 1987).

The opposite way of seeking insight into the processes of memory consists in characterizing biochemically the substances known to affect memory, and then attempting to correlate certain components of their biochemical profile with their effect on memory. The memory-blocking effects of certain antibiotics such as puromycin, anisomycin, and cycloheximide, for instance, inspired a very large number of studies of the possible relations between inhibition of protein synthesis – scientifically the most appealing aspect – and memory (for a review see, for example, *Davies* and *Squire*, 1984). The underlying mode of action has, however, always remained conjectural, because these antibiotics exert many other known

Pharmacopsychiat. 22 (1989) 102–106 (Supplement)

effects (see, for example, *Flexner* and *Goodman*, 1975; *Rainbow* et al., 1979) and quite probably just as many other unknown effects that might equally well be responsible for the disturbance of memory, or at least contribute to it. The possibility that the known biochemical effect under scrutiny may not be responsible for the observed effect on memory, or that that effect may be due to the interplay of several discrete effects, must always be taken into consideration, even in studies using the abovmentioned "specific tools": failure to do so makes false conclusions unavoidable.

One practicable and valid approach to the experimental investigation of mechanisms underlying memory storage, or the regulation of memory storage, may be afforded by the piracetam-like nootropics. These are interesting preparations, above all because they exert distinct, positive effects on various manifestations of memory, yet provoke few or no side-effects. The fact that they have so far been found to display scarcely any effects in most of the traditional assays used in biochemistry laboratories may make them appear all the more or all the less attractive, depending on the viewpoint of the observer. If, however, as has already been suggested (*Giurgea*, 1973, 1982), they do act specifically on cognitive processes or on the structures and mechanisms responsible for cognitive processes, then the elucidation of their mode of action might represent a very significant advance. The following remarks, illustrated by a selection of experimental observations, will be concerned with the progress made to date along this line of research and the possibilities emerging from it.

Neuropharmacological findings

The first experimentally demonstrable effect of piracetam, the prototype substance, on the CNS was inhibition of central nystagmus in the rabbit (*Giurgea* et al., 1967). In retrospect, however, the vast majority of the experimental preclinical findings seem to be indicative of effects on cognitive processes, in particular on learning and memory in a very wide variety of forms. Piracetam, for instance, diminishes the disruptive effect of a cerebral electroshock on the orientation of rats in a water maze (*Giurgea* and *Mouravieff Lesuisse*, 1972). Many other authors have also observed anti-amnestic effects of piracetam and related substances: distinct protective effects against the disturbance of memory following cerebral electroshocks in passive- and active-avoidance tests on mice and rats were noted by *Cumin* et al. (1982) after treatment with aniracetam and piracetam, and by *Mondadori* et al. (1986) after treatment with oxiracetam and piracetam. *Sara* (1980) observed similar responses to etiracetam. *Butler* et al. (1987) described anti-amnestic effects of a whole series of piracetam analogues, including pramiracetam. Numerous observations have also been made of direct positive effects on learning and memory: aniracetam and piracetam (*Yamada* et al., 1985; *Wolthuis*, 1971), etiracetam (*Sara*, 1980) and oxiracetam (*Mondadori* et al., 1986) were found to exert direct effects on acquisition and retention performance in rats and mice in passive- and active-avoidance paradigms; pramiracetam increased the acquisition rate in a 16-armed radial maze (*Murray* and *Fibiger*, 1986) and in a place navigation test (Morris maze) (*Poschel* et al., 1985); positive effects of aniracetam were demonstrated in matching-to-sample tests (*Pontecorvo* et al., 1985). All these findings are supplemented and indirectly supported by observations of a facilitating effect of piracetam on interhemispherical transfer (*Buresova* and *Bures*, 1976), on augmentation of paradoxical sleep in rats (*Wetzel*, 1985), on increased theta power in the hippocampal EEG, and on a reduction in the power of cortical slow waves (*Poschel* et al., 1985).

Interesting and biochemically inexplicable observations indicate that both piracetam and oxiracetam intensify the anticonvulsive effects of anti-epileptics such as carbamazepine (*Mondadori* et al., 1984; *Mondadori* and *Schmutz*, 1986; *Hawkins* and *Mellanby*, 1986).

Biochemical effects of piracetam-like nootropics

There are relatively few data available on the biochemical effects of the piracetam-like nootropics. For a long time, the observation by *Nickolson* and *Wolthuis* (1976) that piracetam stimulates adenylate kinase activity was the sole measured biochemical effect. *Woelk* (1979) then showed that piracetam increased the incorporation of 32P in phosphatidylinositol and phosphatidyl chloride in glia cells and neurons. *Grau* et al. (1987) reported an increase in glucose utilization under hypoxic conditions and accelerated recovery of the EEG. *Poschel* et al. (1983) demonstrated that neither piracetam nor pramiracetam bound to muscarinic cholinergic receptors; nor did binding occur in a dopamine assay with haloperidol. The uptake of GABA and serotonin was not affected by piracetam or by pramiracetam. *Pugsley* et al. (1983) found no evidence of activity in traditional pharmacological assays. No effects were detectable on the concentrations of noradrenaline, dopamine, 5-HT, or 5-HIAA in the cortex or midbrain of the rat. At very high doses (200 mg/kg i.p.), piracetam increased striatal HV without affecting DA levels, indicating that it augments the turnover of DA. Pramiracetam, however, did not increase DA turnover. Receptor assays revealed no affinity of either piracetam or pramiracetam for DA, muscarinic, alpha 1,2- and beta 1,2-adrenergic, 5-HT_1-, 5-HT_2-, GABA, adenosine, and benzodiazepine receptors. On the other hand, it was shown (*Pugsley* et al., 1983; *Shih* and *Pugsley*, 1985) that pramiracetam increased high-affinity choline uptake into hippocampal synaptosomes. The effective doses were 44 and 88 mg/kg i.p.: neither higher nor lower doses were active. Surprisingly enough, piracetam at 100 and 300 mg/kg and aniracetam between 10 and 200 mg/kg both had no effect on high-affinity choline uptake. These results with piracetam are slightly at variance with the observations reported by *Pedata* et al. (1984). These latter authors found that both oxiracetam and piracetam exerted positive effects on high-affinity choline uptake in the rat cortex and hippocampus. The discrepancy may have been due to the timing of the determinations.

The above cholinergic effects are supplemented by findings made by *Spignoli* and *Pepeu* (1986) which demonstrated that oxiracetam prevented the decrease in the acetylcholine content of the cortex and hippocampus induced by cerebral electroshock treatment (piracetam was inactive). Further observations show that piracetam reduces scopolamine-induced amnesia (*Piercey* et al., 1987) and, according to one interesting report (*Pilch* and *Müller*, 1988), elevates the muscarinic cholinergic receptor density in the frontal cortex of aged rats.

Taken as a whole, this selection of findings might at first glance give the impression that the piracetam-like nootropics act by way of cholinergic mechanisms. This conclusion is all the more plausible because there is a very large body of literature on the significance of cholinergic mechanisms in learning and memory (see, for example, *Drachman*, 1978; *Bartus*, 1980). On closer scrutiny of the available results, however, it becomes plainly evident that there is not one single report in which several piracetam-like nootropics tested concurrently have actually been found to produce the same effects. The observed effects, insofar as they have been studied, are not common to all nootropics (*Shih* and *Pugsley*, 1985; *Spignoli* and *Pepeu*, 1986). Considering their similarity in structure as well as in their pharmacological profiles of activity on learning and memory, it seems quite likely (or at least quite possible) that all representatives of this class modulate memory via the same mechanism. Failing any definite evidence to the contrary, this is certainly reason enough to continue the search for one common mechanism of action shared by all the substances belonging to this class.

Are steroids involved in the mediation of nootropic effects?

Even if allowance is made for individual variations dependent on their particular pharmacokinetics, it is still true to say that whenever neuropharmacological agents are administered systemically the brain is flooded with active substance. One may well wonder what chance there is of improving the performance of such a complex and finely tuned organ by so crude a method. On the other hand, there are indications pointing to the existence of endogenous physiological mechanisms that can, under certain circumstances, heigthen the performance of the memory: flash-bulb memories (see e.g. *Brown* and *Kulik*, 1977), i.e. abnormally sharp recollections of certain events mostly associated with highly emotional states, are a good example. If such mechanisms do in fact exist, then they obviously deserve to be regarded as potential targets for pharmacological interventions. In this context, account must also be taken of the possibility that the selective physiological activation of certain neuronal mechanisms in the brain proceeds via peripheral mediators. Nor can one simply dismiss the further possibility that the memory facilitation induced by nootropic drugs may come about through modulation of such processes. Since the pituitary-adrenal axis plays a significant part in emotional states, it seemed important to find out whether piracetam-like nootropics retained their activities in adrenalectomized animals. They did not: oxiracetam, piracetam, aniracetam, and pramiracetam showed no memory-enhancing effects in adrenalectomized mice (*Mondadori* and *Petschke*, 1987). A series of further studies proved that the blockade of their activities was not an effect of dosage: even significantly higher doses of the nootropics were ineffective after adrenalectomy (*Mondadori, Ducret* and *Petschke*, 1989, in press); Accordingly, the next question was whether the products of the adrenal medulla or of the cortex are the critical components in the activity of nootropics. To answer that question the animals were pretreated with aminoglutethimide, which is an inhibitor of several cytochrome-P450-mediated hydroxylation steps in steroid biosynthesis in the adrenal cortex: e.g. 18-hydroxylation of corticosterone (i.e. aldosterone biosynthesis), side-chain cleavage (i.e. conversion of cholesterol to pregnenolone), and 11-hydroxylation (i.e. glucocorticoid biosynthesis) (for a review see *Santen* et al., 1981). Exactly as adrenalectomy, this pretreatment rendered the four piracetam-like nootropics inactive. Aminoglutethimide itself had no effects on the retention performance of the mice. These data provided the first indication of the involvement of products of the adrenal cortex in the mediation of the effects of the piracetam-like nootropics. It must be conceded that aminoglutethimide is not entirely devoid of effects on the adrenal medulla: increases in catecholamine levels have been observed (*Duckworth* and *Kitabchi*, 1971). To exclude this possibility, mice were pretreated with epoxymexrenon. Pretreatment with this specific mineralocorticoid antagonist (*de Gasparo* et al., 1987) gave similar results: the memory-enhancing effects of the piracetam-like nootropics were completely blocked; and again the drug itself had no effect on memory. These findings prove that steroids can play a role in the mediation of nootropic effects. Furthermore, these were the first pharmacological experiments in which all four prototype substances behaved in exactly the same way. (*Mondadori* et al, 1989, in press)

It is interesting to note that certain other substances also lose their memory-modulating activities in the absence of the adrenals: e.g. amphetamine and hydroxyamphetamine (*Martinez* et al., 1980) and vasopressin (*Borell* et al., 1983). However, the effects of these drugs appear to be dependent on the function of the adrenal medulla.

Although autoradiographic studies of the rat brain give the impression that oxiracetam does not readily penetrate the blood-brain barrier (*Mondadori* and *Petschke*, 1987), the above-mentioned findings as a whole cannot be taken as evidence that the piracetam-like nootropics act peripherally. Amongst various other possible mechanisms (see also *Mondadori* and *Petschke*, 1987), it is conceivable that activation of steroid receptors in the brain may be a prerequisite for the efficacy of the piracetam-like nootropics; in other words, steroids may mediate the action of nootropics on memory. The converse is equally plausible, i.e. that these preparations directly or indirectly modulate the effects of certain steroids on memory. There is ample evidence to show that steroids can exert an influence on memory (see for example, *Micheau* et al., 1985; *Bohus* and *de Kloet*, 1981). A new facet emerging from the authors' experiments is that aldosterone-receptor-mediated activity may play a part in memory processing or its regulation.

How these effects come about is unclear; but extrapolation from findings on the peripheral effects of steroids discloses a particularly fascinating aspect. It has been demonstrated that in various organs steroids affect specific gene expression by modulating the rate of transcription of a specific set of genes (*Yamamoto*, 1985; *Schütz*, 1988). It would therefore be extremely interesting to know whether piracetam-like nootropics can exert direct effects on gene transcription, or modulate the action of steroids on gene transcription. There are already a number of publications on the effects of steroids on protein synthesis (*Arenander* and *Vallis*, 1980; *Etgen* et al., 1980; *Nestler* et al., 1981; *Mileusnic* et al., 1986). Since it is known that protein synthesis plays an important part in the formation of memory traces (for a review see *Davies* and

Squire, 1984), it is conceivable that nootropics may improve memory via modulation of protein synthesis.

The present observations, which suggest that steroids may be involved in the mediation of the nootropic action of the piracetam derivatives, do not contradict the reported findings on their cholinergic effects, since the possibility that steroids may interact with cholinergic mechanisms cannot simply be dismissed.

References

Arenander, A., J. Vallis: Glial-released Proteins in Clonal Cultures and their Modulation by Hydrocortisone. Brain Res. 200 (1980) 401–419

Bartus, R. T.: Cholinergic Drug Effects on Memory and Cognition in Animals. Ed. L. W. Poon (1980) 163–180

Bohus, B., E. R. de Kloet: Adrenal Steroids and Extinction Behavior: Antagonism by Progesterone, Deoxycorticosterone and Dexamethasone of a Specific Effect of Corticosteron. Life Sci. 28 (1981) 433–440

Borell, J., E. R. de Kloet, D. H. G. Versteeg, B. Bohus: The Role of Adrenomedullary Catecholamines in the Modulation of Memory by Vasopressin. Dev. Neurosci. 16 (1983) 85–90

Brown, R., J. Kulik: Flashbulb Memories. Cognition 5 (1977) 73–99

Buresová, O., J. Bures: Piracetam-Induced Facilitation of Interhemispheric Transfer of Visual Information in Rats. Psychopharmacologia 46 (1976) 93–102

Butler, D. E., J. D. Leonard, B. W. Caprathe, Y. J. L'Italien, M. R. Pavia, F. M. Hershenson, P. H. Poschel, J. G. Marriott: Amnesia-Reversal Activity of a Series of Cyclic Imides. J. Med. Chemistry 30 (1987) 498–503

...min, R., E. F. Bandle, E. Gamzu, W. E. Haefely: Effects of the Novel Compound Aniracetam (Ro 13-5057) Upon Impaired Learning and Memory in Rodents. Psychopharmacology 78 (1982) 104–111

Davis, H. P., L. R. Squire: Protein Synthesis and Memory: A Review. Psych. Bull. 96 (1984) 518–559

de Gasparo, M., U. Joss, H. P. Ramjoue, S. E. Whitebread, H. Haenni, L. Schenkel, M. Biollaz, J. Grob, P. Wieland, H. U. Wehrli: Three New Epoxy-spironolactone Derivatives: Characterization in Vivo and in Vitro. J. Pharm. Exp. Ther. 240 (1987) 650–656

Drachmann, D. A.: Central cholinergic system and memory. In: Lipton, M. A., A. DiMascio, K. F. Killam (Eds.) Psychopharmacology a Third Generation of Progress. Raven Press, New York (1978) 651–661

Duckworth, W. C., A. E. Kitabchi: Stimulatory Effect of Aminoglutethimide on Phenylathanolamine-N-methyl Transferase (PNMT). Endocrinology 88 (1971) 384–388

Etgen, A. M., M. Martin, R. Gilbert, G. Lynch: Characterization of corticosterone-induced Protein Synthesis in Hippocampal Slices. J. Neurochem. 35 (1980) 598–602

Flexner, L. B., R. H. Goodman: Studies on memory: Inhibitors of protein Synthesis also Inhibit Catecholamine Synthesis. Proc. Nat. Acad. Sci. USA 72 (1975) 4660–4663

Giurgea, C. E., F. Mouravieff-Lesuisse: Effect Facilitateur du Piracetam sur un Apprentissage Répétitif chez le Rat. J. Pharmacol. 3 (1972) 17–30

Giurgea, C. E.: The "Nootropic" Approach to the Pharmacology of the Integrative Activity of the Brain. Cond. Reflex 8 (1973) 108–115

Giurgea, C. E.: The Nootropic Concept and Its Prospective Implications. Drug Develop. Res. 2 (1982) 441–446

Giurgea, C. E., F. Moyensoons, A. A. Emand: A Gaba-Related Hypothesis on the Mechanism of Action of the Antimotion Sickness Drugs. Arch. int. Pharmacodyn. 166 (1967) 379–387

...rau, M., J. L. Montero, J. Balasch: Effect of Piracetam on elektrocorticogram and Local Cerebral Glucose Utilization in the Rat. Gen. Pharmac. 18 (1987) 205–211

Hawkins, C. A., J. H. Mellanby: Piracetam potentiates the antiepileptic action of carbamazepine in chronic experimental limbic epilepsy. Acta Neurol. Scand. (Suppl. 109) 74 (1986) 117–121

Martinez, Jr., J. L., B. J. Vasquez, H. Righter, R. B. Messing, R. A. Jensen, K. C. Liang, J. L. McGaugh: Attenuation of amphetamine-induced enhancement of learning. Brain Res. 195 (1980) 433–443

Micheau, J., C. Destrade, B. Soumireu-Mourat: Time-Dependent Effects of Posttraining Intrahippocampal Injections of Corticosterone on Retention of Appetitive Learning Tasks in Mice. Europ. J. Pharmacol. 106 (1985) 39–46

Mileusnic, R., S. Kanazir, S. Ruzdiji, L. Raki: Effects of Cortisol Treatment on Protein Synthesis in Septum and Hippocampus of Rat brain. Neuroendocrinology 42 (1986) 306–310

Mondadori, C., M. Schmutz, V. Baltzer: Potentiation of the Anticonvulsant Effects of Antiepileptic Drugs by "Nootropics"; a Potential New Therapeutic Approach. Acta Neurol. Scand. 69 (Suppl. 99) (1984) 131–132

Mondadori, C., W. Classen, J. Borkowski, T. Ducret, H. Buerki, A. Schadé: Effects of Oxiracetam on Learning and Memory in Animals: Comparison with Piracetam. Clinical Neuropharmacology 9 (Suppl. 3) (1986) S27–S38

Mondadori, C.: Pharmacology of Memory – Science or Art? In: Mutschler, E., E. Winterfeldt, Weinheim, New York (Eds.) Trends in Medicinal Chemistry (1987). Presented at the Ninth International Symposium on Medicinal Chemistry, Berlin 1986

Mondadori, C., M. Schmutz: Synergistic Effects of Oxiracetam and Piracetam in Combination with Antiepileptic Drugs. Acta Neurol. Scand. (Suppl. 109) 74 (1986) 113–116

Mondadori, C., F. Petschke: Do Piracetam-Like Compounds Act Centrally Via Peripheral Mechanisms? Brain Res. 435 (1987) 310–314

Mondadori, C., L. Weiskrantz, H. Buerki, F. Petschke, G. E. Fagg: NMDA Receptor Antagonists Can Enhance or impair learning performance in Animals. Exp. Brain Res. 75 (1989) 449–456

Mondadori, C., A. Bhatnagar, J. Borkowski, A. Häusler: Involvement of a steroidal components in the mechanism of action of piracetam-like nootropics. Brain Rev, in press

Mondadori, C., T. Ducret, F. Petschke: Blockade of the Nootropic Action of Piracetam-Like Nootropics by Adrenalectomy: an Effect of Dosage? Behavioural Brain Research, in Press, 1989

Morris, R. G. M., E. Anderson, G. S. Lynch, M. Baudry: Selective Impairment of Learning and Blockade of Long-term Potentiation by an N-methyl-D-aspartate Receptor Antagonist. AP5. Nature 319 (1986) 774–776

Murray, C. L., H. C. Fibiger: The effect of Pramiracetam (CI-879) on the Acquisition of a Radial Arm Maze Task. Psychopharmacology 89 (1986) 378–381

Nestler, E., T. C. Rainbow, B. S. McEwen, P. Greengard: Corticosterone Increases the Amount of Protein I, Neuron-specific Phosphoprotein, in Rat Hippocampus. Science 212 (1981) 1162–1164

Nickolson, V. J., O. L. Wolthuis: Effect of the Acquisition-Enhancing Drug Piracetam on Rat Cerebral Energy Metabolism. Comparison with Naftidrofuryl and Methamphetamine. Biochem. Pharmacol. 25 (1976) 2241–2244

Pedata, F., F. Moroni, G. C. Pepeu: Effect of Nootropic Agents on Brain Cholinergic Mechanisms. Clinical Neuropharmacology 7 (Suppl. 1) (1984) 772

Piercey, M. F., G. D. Vogelsang, S. R. Franklin, A. H. Tang: Reversal of scopolamine-induced Amnesia and Alterations in Energy Metabolism by the Nootropic Piracetam: Implications Regarding Identification of Brain Structures Involved in Consolidation of Memory traces. Brain Res. 424 (1987) 1–9

Pilch, H., W. E. Müller: Piracetam Elevates Muscarinic Cholinergic Receptor Density in the Frontal Cortex of Aged but not of Young Mice. Psychopharmacology 94 (1988) 74–78

Pontecorvo, M. J., H. L. Evans: Effects of Aniracetam on Delayed Matching-to-Sample Performance of Monkeys and Pigeons. Pharmacol. Biochem. Behav. 22 (1985) 745–752

Poschel, B. P. H., J. G. Marriott, M. I. Gluckman: Pharmacology of the Cognition Activator Pramiracetam (CI-879). Drugs Exptl. Clin. Res. IX (12) (1983) 853–671

Poschel, B. P. H., P. M. Ho, F. W. Ninteman, M. J. Callahan: Pharmacologic Therapeutic Window of Pramiracetam Demonstrated in

Behavior, EEG, and Single Neuron Firing Rates. Experientia 41 (1985) 1153–1156

Pugsley, T. A., B. P. H. Poschel, D. A. Downs, Y.-H. Shih, M. I. Gluckman: Some Pharmacological and Neurochemical Properties of a New Cognition Activator Agent, Pramiracetam (CI-879). Psychopharmacol. Bull. 19 (1983) 721–726

Rainbow, T. C., P. L. Hoffman, L. B. Flexner: Studies of Memory: A Reevaluation in Mice of the Effects of Inhibitors On The Rate of Synthesis of Cerebral Proteins As Related to Amnesia. Pharmacol. Biochem. Behav. 12 (1979) 79–84

Santen, R. J., E. Samojlik, T. J. Worgul: III. Aminoglutethimide. Product profile. In: Santen, R. J., I. C. Henderson (Eds.) Pharmanual 2. A comprehensive guide to the therapeutic use of aminoglutethimide. Karger, Basel (1981) 101–160

Sara, S. J.: Memory Retrieval Deficits: Alleviation by Etiracetam, a Nootropic Drug. Psychopharmacology 68 (1980) 235–241

Shih, Y.-H., T. A. Pugsley: The effects of Various Cognition-enhancing Drugs on in Vitro Rat Hippocampal Synaptosomal Sodium Dependent High Affinity Choline Uptake. Life Sciences 36 (1985) 2145–2152

Spignoli, G., G. C. Pepeu: Oxiracetam Prevents Electroshock-Induced Decrease in Brain Acetylcholine and Amnesia. Europ. J. Pharmacol. 126 (1986) 253–257

Schütz, G.: Control of Gene Expression by Steroid Hormones. Biol. Chem. 369 (1988) 77–86

Wetzel, W.: Effects of nootropic drugs on the sleep-waking pattern of the rat. Biomed. Biochim. Acta 44, 7/8 (1985) 1211–1217

Woelk, H.: Effects of Piracetam on the Incorporation of ^{32}P into the Phospholipids of Neurons and Glial Cells Isolated from Rabbit Cerebral Cortex. Pharmakopsychiat. 12 (1979) 251–256

Wolthuis, O. L.: Experiments with UCB 6215, A Drug Which Enhances Acquisition in Rats: Its Effects Compared with Those of Metamphetamine. Europ. J. Pharmacol. 16 (1971) 283–297

Yamada, K., T. Inoue, M. Tanaka, T. Furukawa: Prolongation of Latencies for Passive Avoidance Responses in Rats Treated with Aniracetam or Piracetam. Pharmacol. Biochem. Behav. 22 (1985) 645–648

Yamamoto, K. R.: Steroid receptor regulated transcription of specific genes and gene networks. Ann. Rev. Genet. 19 (1985) 209–252

Dr. C. Mondadori

Pharmaceutical Research Department
CIBA-GEIGY Limited
CH-4002 Basel
Switzerland

Picamilon appears to be more effective than Hydergine or vinpocetin in improving blood flow to the cerebral vessels. Picamilon readily crosses the blood-brain barrier to protect neurons against the effects of diminished oxygen flow. It also produces cognitive-enhancing effects.

The combination of these effects provides an entirely new method of dealing safely with several causes of neurological aging. Picamilon is approved as a pharmaceutical product in Russia, but is really a vitamin-like compound consisting of a niacin analog (n-nicotinoyl) uniquely bonded to GABA (gamma aminobutyric acid). When niacin is bound to GABA, it creates a molecule that readily penetrates the blood-brain barrier to enhance cerebral and peripheral circulation. What enables picamilon to work so well is the synergism between the niacin and GABA molecules.

Suggested dose: One tablet, two to three times a day.
If cognitive enhancing results do not occur in 30 days, double the dose.

PIRACETAM

Piracetam is a derivative of the amino acid GABA that increases the sensitivity of receptors in the brain involved in memory and learning. Piracetam is called a nootropic drug because of its ability to enhance the mind. Studies in both animals and humans have demonstrated that Piracetam can improve memory, increase attention and cognition, improve spatial learning, and enhance motor mechanisms. Piracetam is one of the most popular "smart drugs" that is used to increase intelligence, information processing ability, concentration, memory, and creativity. It has been shown to harmonize and synchronize the spheres of the brain by anchoring information within the brain.

Suggested dose: Piracetam should be used in doses ranging from 1600 to 2400 mg a day taken first thing in the morning.

RETIN A

Retin A is a highly publicized vitamin A derivative that stimulates skin cell renewal, increasing the creation of youthful cells at the skin's surface. Retin A may produce side effects such as minor irritation. People using Retin A should stay out of the sun and use a sunblock for normal sunlight exposure, because Retin A increases skin sensitivity to sunlight.

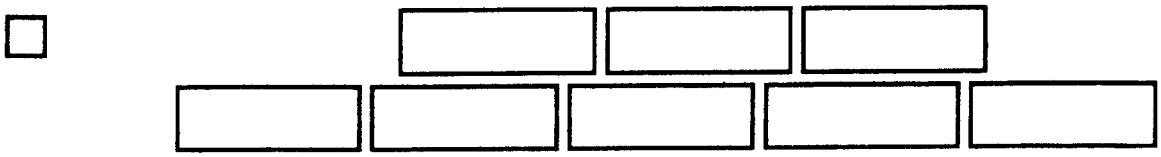
jschoon@clemson.edu

http://www.subnet.co.uk/alpha/aframe.htm

http://www.qhi.co.uk

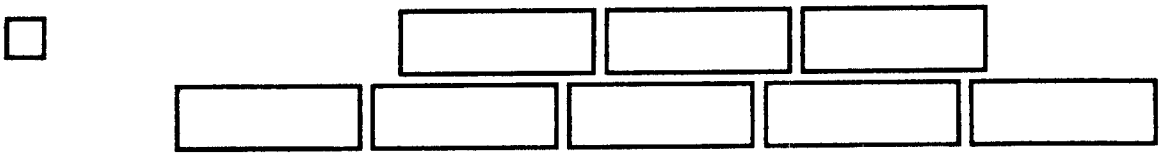
http://www.ers.com/~Nubram/

http://www2.smart.net/~inhome/index.html



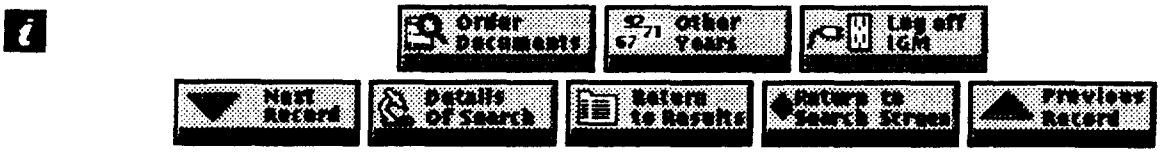
TITLE:	Piracetam-induced changes in the functional activity of neurons as a possible mechanism for the effects of nootropic agents.
AUTHOR:	Verbnyi YaI; Derzhiruk LP; Mogilevskii AYa
AUTHOR AFFILIATION:	Physical-Technical Low Temperature Institute, National Academy of Sciences of Ukraine, Khar'kov.
SOURCE:	Neurosci Behav Physiol 1996 Nov-Dec;26(6):507-15
NLM CIT. ID:	97173873
ABSTRACT:	Studies were carried out on the effects of piracetam (4-20 mM) on the electrical activity of identified neurons in the isolated central nervous system of the pond snail in conditions of single-electrode intracellular stimulation and recording. Piracetam-induced changes were seen in 60-70% of the neurons studied. Different parameters showed different sensitivities to piracetam: the most frequent changes were in the action potential generation threshold, the slope and shape of the steady-state voltage-current characteristics of neuron membranes, and the appearance of piracetam-induced transmembrane ion currents. Nifedipine and cadmium ions, both of which are calcium channel blockers, generally reversed or weakened the effects of piracetam on the changes seen in test cells. This indicates that the effects of piracetam result from its action on calcium channels; selective changes in calcium channels may determine which piracetam-induced effects appear at the cellular level. It is hypothesized that the piracetam-sensitive cellular plasticity mechanisms may make a significant contribution to its nootropic action at the behavioral level.
MAIN MESH SUBJECTS:	Lymnaea/*PHYSIOLOGY Neurons/*DRUG EFFECTS Nootropic Agents/ANTAGONISTS & INHIB/*PHARMACOLOGY Piracetam/ANTAGONISTS & INHIB/*PHARMACOLOGY

ADDITIONAL MESH SUBJECTS:	**Animal** **Cadmium/PHARMACOLOGY** **Calcium Channel Blockers/PHARMACOLOGY** **Electrophysiology** **Ganglia, Invertebrate/CYTOLOGY/PHYSIOLOGY** **In Vitro** **Membrane Potentials/DRUG EFFECTS/PHYSIOLOGY** **Nifedipine/PHARMACOLOGY** **Parietal Lobe/CYTOLOGY/DRUG EFFECTS** **Patch-Clamp Techniques**
PUBLICATION TYPES:	**JOURNAL ARTICLE**
LANGUAGE:	**Eng**
REGISTRY NUMBERS:	**0 (Calcium Channel Blockers)** **0 (Nootropic Agents)** **21829-25-4 (Nifedipine)** **7440-43-9 (Cadmium)** **7491-74-9 (Piracetam)**



TITLE:	Nootropic drugs and brain cholinergic mechanisms.
AUTHOR:	Pepeu G; Spignoli G
AUTHOR AFFILIATION:	Department of Preclinical and Clinical Pharmacology, University of Florence, Italy.
SOURCE:	Prog Neuropsychopharmacol Biol Psychiatry 1989;13 Suppl:S77-88
NLM CIT. ID:	90139561
ABSTRACT:	1. This review has two aims: first, to marshal and discuss evidences demonstrating an interaction between nootropic drugs and brain cholinergic mechanisms; second, to define the relationship between the effects on cholinergic mechanisms and the cognitive process. 2. Direct or indirect evidences indicating an activation of cholinergic mechanisms exist for pyrrolidinone derivatives including piracetam, oxiracetam, aniracetam, pyroglutamic acid, tenilsetam and pramiracetam and for miscellaneous chemical structures such as vinpocetine, naloxone, ebiratide and phosphatidylserine. All these drugs prevent or revert scopolamine-induced disruption of several learning and memory paradigms in animal and man. 3. Some of the pyrrolidinone derivatives also prevent amnesia associated with inhibition of acetylcholine synthesis brought about by hemicholinium. Oxiracetam prevents the decrease in brain acetylcholine and amnesia caused by electroconvulsive shock. Oxiracetam, aniracetam and pyroglutamic acid prevent brain acetylcholine decrease and amnesia induced by scopolamine. Comparable bell-shaped dose-effect relationships result for both actions. Phosphatidylserine restores acetylcholine synthesis and conditioned responses in aging rats. 4. The mechanisms through which the action on cholinergic systems might take place, including stimulation of the high affinity choline uptake, are discussed. The information available are not yet sufficient to define at which steps of the cognitive process the action on cholinergic system plays a role and which are the influences of the changes in cholinergic function on other neurochemical mechanisms of learning and memory.
MAIN MESH SUBJECTS:	Acetylcholine/*METABOLISM Brain/DRUG EFFECTS/*METABOLISM Psychotropic Drugs/*PHARMACOLOGY

ADDITIONAL MESH SUBJECTS:	**Animal** **Receptors, Cholinergic/DRUG EFFECTS/METABOLISM** **Scopolamine/PHARMACOLOGY** **Synapses/DRUG EFFECTS/PHYSIOLOGY**
PUBLICATION TYPES:	**JOURNAL ARTICLE** **REVIEW** **REVIEW, TUTORIAL**
LANGUAGE:	**Eng**
REGISTRY NUMBERS:	**0 (Receptors, Cholinergic)** **51-34-3 (Scopolamine)** **51-84-3 (Acetylcholine)**



TITLE:	Piracetam elevates muscarinic cholinergic receptor density in the frontal cortex of aged but not of young mice.
AUTHOR:	Pilch H; Muller WE
AUTHOR AFFILIATION:	Psychopharmacological Laboratory, Central Institute of Mental Health, Mannheim, Federal Republic of Germany.
SOURCE:	Psychopharmacology (Berl) 1988;94(1):74-8
NLM CIT. ID:	88158509
ABSTRACT:	Chronic treatment (2 weeks) with piracetam (500 mg/kg, once daily PO) elevated m-cholinoceptor density in the frontal cortex of aged (18 months) female mice by about 30-40%, but had no effect on m-cholinoceptor density in the frontal cortex of young (4 weeks) mice. The effect of piracetam on m-cholinoceptor density as determined by the specific binding of tritiated QNB was not affected by concomitant daily treatment with either choline (200 mg/kg) or scopolamine (4 mg/kg). It is concluded that the effect of piracetam on m-cholinoceptor density could explain the positive effects which have been reported for combinations of cholinergic precursor treatment with piracetam on memory and other cognitive functions in aged experimental animals and patients and could also represent part of the possible mechanism of action of piracetam alone.
MAIN MESH SUBJECTS:	Aging/*METABOLISM Cerebral Cortex/DRUG EFFECTS/*METABOLISM Piracetam/*PHARMACOLOGY Pyrrolidinones/*PHARMACOLOGY Receptors, Muscarinic/*DRUG EFFECTS
ADDITIONAL MESH SUBJECTS:	Animal Atropine/PHARMACOLOGY Female Male Mice Oxotremorine/PHARMACOLOGY Quinuclidinyl Benzilate/PHARMACOLOGY Scopolamine/PHARMACOLOGY

PUBLICATION TYPES:	**JOURNAL ARTICLE**
LANGUAGE:	**Eng**
REGISTRY NUMBERS:	**0 (Pyrrolidinones)** **0 (Receptors, Muscarinic)** **51-34-3 (Scopolamine)** **51-55-8 (Atropine)** **6581-06-2 (Quinuclidinyl Benzilate)** **70-22-4 (Oxotremorine)** **7491-74-9 (Piracetam)**

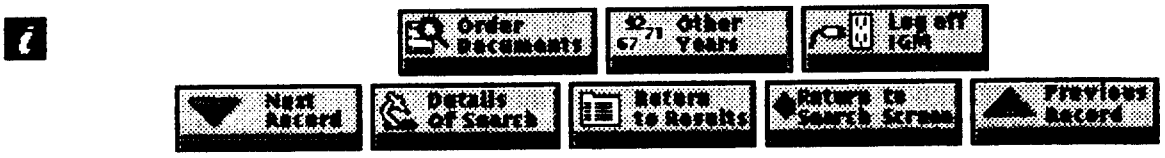
STROK

TITLE:	**Treatment of acute ischemic stroke with piracetam. Members of the Piracetam in Acute Stroke Study (PASS) Group.**
AUTHOR:	**De Deyn PP; Reuck JD; Deberdt W; Vlietinck R; Orgogozo JM**
AUTHOR AFFILIATION:	**Department of Neurology, Middelheim Hospital, Antwerp, Belgium.**
SOURCE:	**Stroke 1997 Dec;28(12):2347-52**
NLM CIT. ID:	**98074088**

ABSTRACT: BACKGROUND AND PURPOSE: Piracetam, a nootropic agent with neuroprotective properties, has been reported in pilot studies to increase compromised regional cerebral blood flow in patients with acute stroke and, given soon after onset, to improve clinical outcome. We performed a multicenter, randomized, double-blind trial to test whether piracetam conferred benefit when given within 12 hours of the onset of acute ischemic stroke to a large group of patients. METHODS: Patients received placebo or 12 g piracetam as an initial intravenous bolus, 12 g daily for 4 weeks and 4.8 g daily for 8 weeks. The primary end point was neurologic outcome after 4 weeks as assessed by the Orgogozo scale. Functional status at 12 weeks as measured by the Barthel Index was the major secondary outcome. CT scan was performed within 24 hours of the onset of stroke but not necessarily before treatment. Analyses based on the intention to treat were performed in all randomized patients (n = 927) and in an "early treatment" population specified in the protocol as treatment within 6 hours of the onset of stroke but subsequently redefined as less than 7 hours after onset (n = 452). RESULTS: In the total population, outcome was similar with both treatments (the mean Orgogozo scale after 4 weeks: piracetam 57.7, placebo 57.6; the mean Barthel Index after 12 weeks: piracetam 55.8, placebo 53.1). Mortality at 12 weeks was 23.9% (111/464) in the piracetam group and 19.2% (89/463) in the placebo group (relative risk 1.24, 95% confidence interval, 0.97 to 1.59; P = .15). Deaths were fewer in the piracetam group in those patients in the intention-to-treat population admitted with primary hemorrhagic stroke. Post hoc analyses in the early treatment subgroup showed differences favoring piracetam relative to placebo in mean Orgogozo scale scores after 4 weeks (piracetam 60.4, placebo 54.9; P = .07) and Barthel Index scores at 12 weeks (piracetam 58.6, placebo 49.4; P = .02). Additional analyses within this subgroup, confined to 360 patients with moderate and severe stroke (initial Orgogozo scale score < 55), showed significant improvement on piracetam in both outcomes (P < .02). CONCLUSIONS: Piracetam did not influence outcome when given within 12 hours of the onset of acute ischemic stroke. Post hoc analyses suggest that piracetam may confer benefit when given within 7 hours of onset, particularly in patients with stroke of moderate and severe degree. A randomized, placebo-controlled, multicenter study, the Piracetam Acute Stroke Study II (PASS II) will soon begin.

MAIN MESH SUBJECTS:
Cerebral Ischemia/*DRUG THERAPY/MORTALITY
Cerebrovascular Disorders/*DRUG THERAPY/MORTALITY
Neuroprotective Agents/ADVERSE EFFECTS/*THERAPEUTIC USE
Nootropic Agents/ADVERSE EFFECTS/*THERAPEUTIC USE
Piracetam/ADVERSE EFFECTS/*THERAPEUTIC USE

ADDITIONAL MESH SUBJECTS:	**Acute Disease** **Aged** **Aged, 80 and over** **Double-Blind Method** **Female** **Human** **Male** **Middle Age** **Support, Non-U.S. Gov't** **Survival Analysis** **Treatment Outcome**
PUBLICATION TYPES:	**CLINICAL TRIAL** **JOURNAL ARTICLE** **MULTICENTER STUDY** **RANDOMIZED CONTROLLED TRIAL**
LANGUAGE:	**Eng**
REGISTRY NUMBERS:	**0 (Neuroprotective Agents)** **0 (Nootropic Agents)** **7491-74-9 (Piracetam)**



dyslexia

TITLE:	The effects of piracetam in children with dyslexia.
AUTHOR:	Di Ianni M; Wilsher CR; Blank MS; Conners CK; Chase CH; Funkenstein HH; Helfgott E; Holmes JM; Lougee L; Maletta GJ; et al
SOURCE:	J Clin Psychopharmacol 1985 Oct;5(5):272-8
NLM CIT. ID:	86009005
ABSTRACT:	Following previous research which suggests that piracetam improves performance on tasks associated with the left hemisphere, a 12-week, double-blind, placebo-controlled study of developmental dyslexics was conducted. Six study sites treated 257 dyslexic boys between the ages of 8 and 13 years who were significantly below their potential in reading performance. Children were of at least normal intelligence, had normal findings on audiologic, ophthalmologic, neurologic, and physical examination, and were neither educationally deprived nor emotionally disturbed. Piracetam was found to be well tolerated in this study population. Children treated with piracetam showed improvements in reading speed. No other effects on reading were observed. In addition, improvement in auditory sequential short-term memory was observed in those piracetam-treated patients who showed relatively poor memory at baseline. It is suggested that longer term treatment with piracetam may result in additional improvement.
MAIN MESH SUBJECTS:	Dyslexia/*DRUG THERAPY Piracetam/ADVERSE EFFECTS/*THERAPEUTIC USE Pyrrolidinones/*THERAPEUTIC USE
ADDITIONAL MESH SUBJECTS:	Adolescence Child Clinical Trials Depression/CHEMICALLY INDUCED Human Male Memory Disorders/DRUG THERAPY Memory, Short-Term Support, Non-U.S. Gov't
PUBLICATION TYPES:	CLINICAL TRIAL CONTROLLED CLINICAL TRIAL JOURNAL ARTICLE RANDOMIZED CONTROLLED TRIAL
LANGUAGE:	Eng
REGISTRY NUMBERS:	0 (Pyrrolidinones) 7491-74-9 (Piracetam)

TITLE:	Piracetam and dyslexia: effects on reading tests.
AUTHOR:	Wilsher CR; Bennett D; Chase CH; Conners CK; DiIanni M; Feagans L; Hanvik LJ; Helfgott E; Koplewicz H; Overby P; et al
SOURCE:	J Clin Psychopharmacol 1987 Aug;7(4):230-7
NLM CIT. ID:	87308901
ABSTRACT:	Previous research has suggested that dyslexics treated with piracetam have shown improvements in reading skills, verbal memory and verbal conceptualizing ability, feature analysis and processing of letter-like stimuli. Two hundred twenty-five dyslexic children between the ages of 7 years 6 months and 12 years 11 months whose reading skills were significantly below their intellectual capacity were enrolled in a multicenter, 36-week, double-blind, placebo-controlled study. Children of below average intelligence, with abnormal findings on audiologic, ophthalmologic, neurologic, psychiatric, and physical examinations, who were emotionally disturbed or educationally deprived and who had recently been treated with psychoactive medication were excluded from the trial. Piracetam was well tolerated, with no serious adverse clinical or laboratory effects reported. Piracetam-treated children showed significant improvements in reading ability (Gray Oral Reading Test) and reading comprehension (Gilmore Oral Reading Test). Treatment effects were evident after 12 weeks and were sustained for the total period (36 weeks).
MAIN MESH SUBJECTS:	Dyslexia/*DRUG THERAPY/PSYCHOLOGY Piracetam/ADVERSE EFFECTS/*THERAPEUTIC USE Pyrrolidinones/*THERAPEUTIC USE *Reading
ADDITIONAL MESH SUBJECTS:	Child Clinical Trials Double-Blind Method Female Human Male Random Allocation Support, Non-U.S. Gov't
PUBLICATION TYPES:	CLINICAL TRIAL CONTROLLED CLINICAL TRIAL JOURNAL ARTICLE RANDOMIZED CONTROLLED TRIAL
LANGUAGE:	Eng
REGISTRY NUMBERS:	0 (Pyrrolidinones) 7491-74-9 (Piracetam)

http://130.14.32.42/cgi-bin/NGM-client/10738+detail+2

cognition

☑

TITLE:	An overview of pharmacologic treatment of cognitive decline in the aged.
AUTHOR:	Reisberg B; Ferris SH; Gershon S
SOURCE:	Am J Psychiatry 1981 May;138(5):593-600
NLM CIT. ID:	81204750
ABSTRACT:	The most widely known substances that have been investigated for treating cognitive deterioration in the aged are cerebral vasodilators, Gerovital H3, psychostimulants, "nootropics," neuropeptides, and neurotransmitters. The rationale for the choice of specific agents has shifted as our conceptions regarding the origins of cognitive decline have changed; we now know that most cognitive deterioration occurs independently of arteriosclerotic vascular changes. Substances currently being investigated because of their effects on brain electrophysiology, on neurohumoral processes, or on central neurotransmitters show promise.
MAIN MESH SUBJECTS:	Cognition Disorders/*DRUG THERAPY
ADDITIONAL MESH SUBJECTS:	Anticoagulants/THERAPEUTIC USE Clinical Trials Comparative Study Dihydroergotoxine/THERAPEUTIC USE Human Hyperbaric Oxygenation Methylphenidate/THERAPEUTIC USE Parasympathomimetics/THERAPEUTIC USE Peptides/THERAPEUTIC USE Piracetam/THERAPEUTIC USE Procaine/THERAPEUTIC USE Support, U.S. Gov't, P.H.S. Vasodilator Agents/THERAPEUTIC USE
PUBLICATION TYPES:	CLINICAL TRIAL JOURNAL ARTICLE REVIEW
LANGUAGE:	Eng
REGISTRY NUMBERS:	0 (Anticoagulants) 0 (Parasympathomimetics) 0 (Peptides) 0 (Vasodilator Agents) 11032-41-0 (Dihydroergotoxine) 113-45-1 (Methylphenidate) 12663-50-2 (Gerovital H3) 59-46-1 (Procaine) 7491-74-9 (Piracetam)

National Library of Medicine: IGM Full Record Screen

TITLE: Profound effects of combining choline and piracetam on memory enhancement and cholinergic function in aged rats.

AUTHOR: Bartus RT; Dean RL 3d; Sherman KA; Friedman E; Beer B

SOURCE: Neurobiol Aging 1981 Summer;2(2):105-11

NLM CIT. ID: 82058347

http://130.14.32.42/cgi-bin/IGM-Client:10738+detail+2

ABSTRACT: In an attempt to gain some insight into possible approaches to reducing age-related memory disturbances, aged Fischer 344 rats were administered either vehicle, choline, piracetam or a combination of choline or piracetam. Animals in each group were tested behaviorally for retention of a one trial passive avoidance task, and biochemically to determine changes in choline and acetylcholine levels in hippocampus, cortex and striatum. Previous research has shown that rats of this strain suffer severe age-related deficits on this passive avoidance task and that memory disturbances are at least partially responsible. Those subjects given only choline (100 mg/kg) did not differ on the behavioral task from control animals administered vehicle. Rats given piracetam (100 mg/kg) performed slightly better than control rats (p less than 0.05), but rats given the piracetam/choline combination (100 mg/kg of each) exhibited retention scores several times better than those given piracetam alone. In a second study, it was shown that twice the dose of piracetam (200 mg/kg) or choline (200 mg/kg) alone, still did not enhance retention nearly as well as when piracetam and choline (100 mg/kg of each) were administered together. Further, repeated administration (1 week) of the piracetam/choline combination was superior to acute injections. Regional determinations of choline and acetylcholine revealed interesting differences between treatments and brain area. Although choline administration raised choline content about 50% in striatum and cortex, changes in acetylcholine levels were much more subtle (only 6-10%). No significant changes following choline administration were observed in the hippocampus. However, piracetam alone markedly increased choline content in hippocampus (88%) and tended to decrease acetylcholine levels (19%). No measurable changes in striatum or cortex were observed following piracetam administration. The combination of choline and piracetam did not potentiate the effects seen with either drug alone, and in certain cases the effects were much less pronounced under the drug combination. These data are discussed as they relate to possible effects of choline and piracetam on cholinergic transmission and other neuronal function, and how these effects may reduce specific memory disturbances in aged subjects. The results of these studies demonstrate that the effects of combining choline and piracetam are quite different than those obtained with either drug alone and support the notion that in order to achieve substantial efficacy in aged subjects it may be necessary to reduce multiple, interactive neurochemical dysfunctions in the brain, or affect activity in more than one parameter of a deficient metabolic pathway.

MAIN MESH SUBJECTS:
*Aging
Choline/ANALYSIS/*PHARMACOLOGY
Memory/*DRUG EFFECTS
Parasympathetic Nervous System/*PHYSIOLOGY
Piracetam/*PHARMACOLOGY
Pyrrolidinones/*PHARMACOLOGY

http://130.14.32.42/cgi-bin/ICM-client?10738+detail+2

ADDITIONAL MESH SUBJECTS:	**Acetylcholine/ANALYSIS/SECRETION** **Animal** **Brain Chemistry/DRUG EFFECTS** **Male** **Rats** **Rats, Inbred F344**
PUBLICATION TYPES:	**JOURNAL ARTICLE**
LANGUAGE:	**Eng**
REGISTRY NUMBERS:	**0 (Pyrrolidinones)** **51-84-3 (Acetylcholine)** **62-49-7 (Choline)** **7491-74-9 (Piracetam)**

http://130.14.32.42/cgi-bin/IGM-client/10738+detail+1

National Library of Medicine: IGM Full Record Screen

TITLE: Piracetam-induced facilitation of interhemispheric transfer of visual information in rats.

AUTHOR: Buresova O; Bures J

SOURCE: Psychopharmacologia 1976;46(1):93-102

NLM CIT. ID: 76152798

ABSTRACT: The effect of Piracetam (UCB 6215, 2-pyrrolidoneacetamide) on learning mediated by transcommissural information flow was studied in hooded rats. Acquisition of monocular pattern discrimination was faster in drug-treated rats (100 mg/kg, 30 min before training) than in untreated controls. Subsequent relearning with one hemisphere functionally eliminated by cortical spreading depression showed that the strength of the primary engram formed under Piracetam in the hemisphere contralateral to the trained eye remained unaffected but that the secondary trace (in the ipsilateral hemisphere) was considerably improved and almost equalled the primary one (savings increased from 20-30% to 50-60%). Learning with uncrossed optic fibers was unaffected by the drug. Interhemispheric transfer of lateralized visual engrams acquired during functional hemidecortication was facilitated by Piracetam administration preceding the five transfer trials performed with the untrained eye open (imperative transfer). Piracetam was ineffective when the trained eye was open during transfer trials (facultative transfer). After a visual engram had been lateralized by 5 days of monocular overtraining, Piracetam facilitated formation of the secondary engram induced by 3 interocular transfer trials. It is concluded that Piracetam enhances transcommissural encoding mechanisms activated in the initial stage of monocular learning and in some forms of interhemispheric transfer, but does not affect the transcommissural readout. This effect is interpreted as a special case of the Piracetam-induced facilitation of the phylogenetically old mechanisms of redundant information storage which improve liminal or subnormal learning.

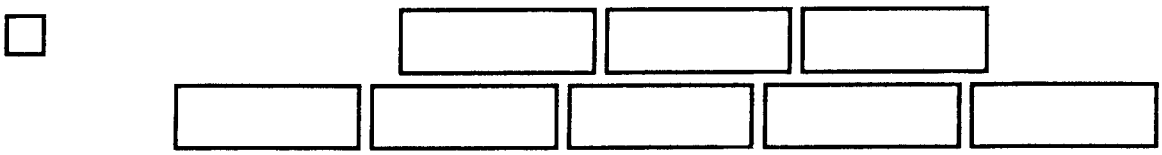
MAIN MESH SUBJECTS:	**Form Perception/*DRUG EFFECTS** **Pattern Recognition, Visual/*DRUG EFFECTS** **Piracetam/*PHARMACOLOGY** **Pyrrolidinones/*PHARMACOLOGY** **Transfer (Psychology)/*DRUG EFFECTS**
ADDITIONAL MESH SUBJECTS:	**Animal** **Corpus Callosum/PHYSIOLOGY** **Discrimination Learning/DRUG EFFECTS** **Male** **Memory/DRUG EFFECTS** **Overlearning/DRUG EFFECTS** **Perceptual Masking** **Rats** **Spreading Cortical Depression**
PUBLICATION TYPES:	**JOURNAL ARTICLE**
LANGUAGE:	**Eng**

http://130.14.32.42/cgi-bin/IGM+Client+10736+detail+1

☑

TITLE:	Some effects of piracetam (UCB 6215, Nootropyl) on chronic schizophrenia.
AUTHOR:	Dimond SJ; Scammell RE; Pryce IG; Huws D; Gray C
SOURCE:	Psychopharmacology (Berl) 1979 Sep;64(3):341-8
NLM CIT. ID:	80057401
ABSTRACT:	A study is described of effects of a nootropic drug on chronic schizophrenia. The nootropic drugs act on the central nervous system with the cerebral cortex as their target. Chronic schizophrenic patients on the drug showed improvement in object naming and in tests where the patient was required to indicate the number of times he had been tapped. Improvements were also noted in learning and memory tasks. In dichotic listening the patients showed a reduction in the amount of incorrect verbal responses produced. There were no improvements in symptom rating or social behaviour rating. These results suggest some cognitive improvement but little if any change in the disease state of the patient.
MAIN MESH SUBJECTS:	Piracetam/*THERAPEUTIC USE Pyrrolidinones/*THERAPEUTIC USE Schizophrenia/*DRUG THERAPY
ADDITIONAL MESH SUBJECTS:	Adult Chronic Disease Clinical Trials Dichotic Listening Tests Double-Blind Method Female Human Male Middle Age Motor Skills/DRUG EFFECTS Psychiatric Status Rating Scales Schizophrenic Psychology
PUBLICATION TYPES:	CLINICAL TRIAL JOURNAL ARTICLE
LANGUAGE:	Eng

National Library of Medicine: IGM Full Record Screen



TITLE:	**Increase in the power of human memory in normal man through the use of drugs.**
AUTHOR:	**Dimond SJ; Brouwers EM**
SOURCE:	**Psychopharmacology (Berl) 1976 Sep 29;49(3):307-9**
NLM CIT. ID:	**77079535**
ABSTRACT:	**Nootropyl (Piracetam) a drug reported to facilitate learning in animals was tested for its effect on man by administering it to normal volunteers. The subjects were given 3x4 capsules at 400 mg per day, in a double blind study. Each subject learned series of words presented as stimuli upon a memory drum. No effects were observed after 7 days but after 14 days verbal learning had significantly increased.**
MAIN MESH SUBJECTS:	**Memory/*DRUG EFFECTS Piracetam/*PHARMACOLOGY Pyrrolidinones/*PHARMACOLOGY**
ADDITIONAL MESH SUBJECTS:	**Female Human Male Stimulation, Chemical Verbal Learning/DRUG EFFECTS**
PUBLICATION TYPES:	**CLINICAL TRIAL CONTROLLED CLINICAL TRIAL JOURNAL ARTICLE**
LANGUAGE:	**Eng**

National Library of Medicine: IGM Full Record Screen

TITLE:	Piracetam facilitates retrieval but does not impair extinction of bar-pressing in rats.
AUTHOR:	Sara SJ; David-Remacle M; Weyers M; Giurgea C
SOURCE:	Psychopharmacology (Berl) 1979 Mar 14;61(1):71-5
NLM CIT. ID:	79180683
ABSTRACT:	Rats were trained on a continuously reinforced bar-press response for water reward. Seven days later they were retested for retention, with or without pretest injection of the nootropic drug, piracetam. Drug-treated animals had significantly shorter response latencies than saline-treated animals. The results are interpreted as a facilitation of retrieval processes after forgetting. The experiment was extended under extinction conditions and it was found that after three sessions there was a tendency to facilitate extinction when response latency is used as the extinction index. The clinical interest of a drug which facilitates the retrieval aspect of the memory process without impairing extinction is discussed.
MAIN MESH SUBJECTS:	Conditioning, Operant/*DRUG EFFECTS Extinction (Psychology)/*DRUG EFFECTS Memory/*DRUG EFFECTS Piracetam/*PHARMACOLOGY Pyrrolidinones/*PHARMACOLOGY
ADDITIONAL MESH SUBJECTS:	Animal Male Rats Water Deprivation
PUBLICATION TYPES:	JOURNAL ARTICLE
LANGUAGE:	Eng

http://130.14.32.40/cgi-bin/ROM-client?19819+detail=33

☑

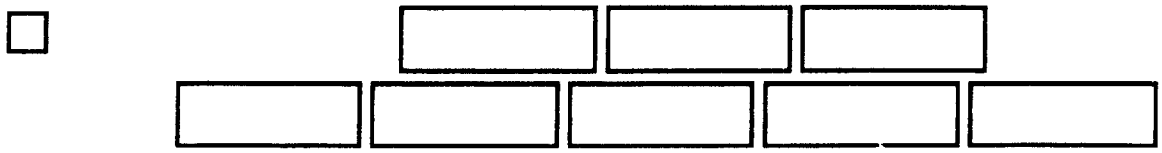
TITLE:	**Piracetam impedes hippocampal neuronal loss during withdrawal after chronic alcohol intake.**
AUTHOR:	**Brandao F; Paula-Barbosa MM; Cadete-Leite A**
AUTHOR AFFILIATION:	**Department of Anatomy, Porto Medical School, Portugal.**
SOURCE:	**Alcohol 1995 May-Jun;12(3):279-88**
NLM CIT. ID:	**95367208**
ABSTRACT:	**In previous studies we have demonstrated that prolonged ethanol consumption induced hippocampal neuronal loss. In addition, we have shown that withdrawal after chronic alcohol intake augmented such degenerative activity leading to increased neuronal death in all subregions of the hippocampal formation but in the CA3 field. In an attempt to reverse this situation, we tested, during the withdrawal period, the effects of piracetam (2-oxo-1-pyrrolidine acetamide), a cyclic derivative of gamma-aminobutyric acid, as there is previous evidence that it might act as a neuronoprotective agent. The total number of dentate granule, hilar, and CA3 and CA1 pyramidal cells of the hippocampal formation were estimated using unbiased stereological methods. We found out that in animals treated with piracetam the numbers of dentate granule, hilar, and CA1 pyramidal cells were significantly higher than in pure withdrawn animals, and did not differ from those of alcohol-treated rats that did not undergo withdrawal. These data suggest that piracetam treatment impedes, during withdrawal, the pursuing of neuronal degeneration.**
MAIN MESH SUBJECTS:	**Ethanol/*ADVERSE EFFECTS** **Hippocampus/*DRUG EFFECTS/PATHOLOGY** **Neurons/*DRUG EFFECTS** **Piracetam/*PHARMACOLOGY** **Substance Withdrawal Syndrome/*PATHOLOGY**
ADDITIONAL MESH SUBJECTS:	**Analysis of Variance** **Animal** **Cell Count/DRUG EFFECTS** **Diet** **Male** **Rats** **Rats, Sprague-Dawley** **Support, Non-U.S. Gov't**
PUBLICATION TYPES:	**JOURNAL ARTICLE**
LANGUAGE:	**Eng**
REGISTRY NUMBERS:	**64-17-5 (Ethanol)** **7491-74-9 (Piracetam)**

http://130.14.32.47/cgi-bin/IGM-client/23694+detail+2

TITLE:	Does piracetam counteract the ECT-induced memory dysfunctions in depressed patients?
AUTHOR:	Mindus P; Cronholm B; Levander SE
SOURCE:	Acta Psychiatr Scand 1975 Jun;51(5):319-26
NLM CIT. ID:	75201625
ABSTRACT:	A double-blind, intra-individual cross-over comparison of the effect of piracetam on retrograde memory impairement as measured by the KS memory test battery was performed in connection with second and third Bi-ECT in 18 patients diagnosed as suffering from depression. The seizure duration and the post-ECT EGG patterns were examined visually and the post-ECT confusion time was measured. Piracetam was given orally in the dose of 4.8 g/day for 3 days. No significant effects were obtained on memory scores, electrical stimulus duration, EEG pattern or post-ECT confusion time. The findings may indicate that the protective effect of piracetam shown in animal electroconvuslive stimulation (ECS) is due to a counteraction of the disturbing effect of hypoxia on memory functions. It is concluded that more information is needed as regards the pharmacokinetics and the mode of action of the drug.
MAIN MESH SUBJECTS:	Depression/*THERAPY Electroconvulsive Therapy/*ADVERSE EFFECTS Memory/*DRUG EFFECTS Memory Disorders/*ETIOLOGY/PREVENTION & CONTROL Piracetam/*PHARMACOLOGY/THERAPEUTIC USE Pyrrolidinones/*PHARMACOLOGY
ADDITIONAL MESH SUBJECTS:	Adult Aged Clinical Trials Drug Evaluation English Abstract Female Human Male Middle Age Placebos
PUBLICATION TYPES:	CLINICAL TRIAL CONTROLLED CLINICAL TRIAL JOURNAL ARTICLE
LANGUAGE:	Eng

TITLE:	Effects of oxiracetam on learning and memory in animals: comparison with piracetam.
AUTHOR:	Mondadori C; Classen W; Borkowski J; Ducret T; Buerki H; Schade A
SOURCE:	Clin Neuropharmacol 1986;9 Suppl 3:S27-38
NLM CIT. ID:	87244092
ABSTRACT:	The effects of oxiracetam and piracetam were compared in learning and memory tests in rats and mice. In the dose range examined, the two nootropics were equally active in reducing the amnesia induced by cerebral electroshock in the mouse. Step-down retention performance, however, was distinctly improved by oxiracetam but unaffected by piracetam, no matter whether it was given before or immediately after the learning trial. Oxiracetam also improved acquisition performance in aged (24- to 27-month-old) rats in an active-avoidance situation at doses of 30 and 100 mg/kg i.p. whereas piracetam showed no effect at 100 mg/kg i.p.
MAIN MESH SUBJECTS:	Avoidance Learning/*DRUG EFFECTS Memory/*DRUG EFFECTS Piracetam/*PHARMACOLOGY Pyrrolidines/*PHARMACOLOGY Pyrrolidinones/*PHARMACOLOGY
ADDITIONAL MESH SUBJECTS:	Aging/PHYSIOLOGY Animal Comparative Study Drug Administration Schedule Electroshock Mice Rats
PUBLICATION TYPES:	JOURNAL ARTICLE
LANGUAGE:	Eng
REGISTRY NUMBERS:	0 (Pyrrolidines) 0 (Pyrrolidinones) 62613-82-5 (oxiracetam) 7491-74-9 (Piracetam)

National Library of Medicine: IGM Full Record Screen



TITLE:	**Effect of chronic treatment with piracetam and tacrine on some changes caused by thymectomy in the rat brain.**
AUTHOR:	**Song C; Earley B; Leonard BE**
AUTHOR AFFILIATION:	**Department of Pharmacology, University College Galway, Ireland.**
SOURCE:	**Pharmacol Biochem Behav 1997 Apr;56(4):697-704**
NLM CIT. ID:	**97276543**

ABSTRACT: Thymectomized rats, 5 weeks after surgery, showed a significant impairment in learning and memory as shown by deficits in passive avoidance and in the Morris water maze test. The behaviour of the thymectomized rats in the "open field" apparatus was largely unchanged. Following treatment for 20 days with either piracetam (500 mg/kg) or tacrine (3.0 mg/kg), the deficit in passive avoidance learning was largely reversed. Chronic treatment with tacrine also reversed the deficit in the behaviour of the thymectomized rats in the Morris water maze. The effects of thymectomy on the biogenic amines and some of their metabolites in the amygdaloid cortex, hypothalamus, striatum and olfactory bulbs were also determined. Relative to the sham-operated controls, thymectomy resulted in a reduction in the noradrenaline concentration in the amygdala, hypothalamus, and olfactory bulbs. This effect was reversed by chronic piracetam and tacrine treatments. The concentration of dopamine was also reduced in the olfactory bulbs after thymectomy whereas in the striatum the concentration of 5-hydroxytryptamine (5-HT; serotonin) was increased. The concentration of gamma amino butyric acid (GABA) was determined in amygdaloid cortex and hippocampus only. The only significant change occurred following chronic treatment of thymectomized rats with tacrine, when a significant elevation of GABA was found. Neither piracetam nor tacrine produced any change in the amines of their metabolites in the sham-operated controls. Tacrine, however, elevated the dopamine and reduced the 5-HT content of the hypothalamus and increased the 3,4-dihydroxylphenylacetic acid concentration of the striatum of thymectomized rats. Examination of the differential white blood cell count of the thymectomized rats showed that the percentage of lymphocytes was decreased, and the percentage of neutrophils increased, relative to the sham-operated controls. Chronic lacrine, but not piracetam, treatment reversed the lesion-induced changes.

MAIN MESH SUBJECTS:
Behavior, Animal/*DRUG EFFECTS
Brain/DRUG EFFECTS/*METABOLISM
Nootropic Agents/*PHARMACOLOGY
Piracetam/*PHARMACOLOGY
Tacrine/*PHARMACOLOGY
Thymus Gland/*IMMUNOLOGY

ADDITIONAL MESH SUBJECTS:
Animal
Avoidance Learning/DRUG EFFECTS
Corticosterone/BLOOD
Leukocyte Count/DRUG EFFECTS
Male
Maze Learning/DRUG EFFECTS
Neurotransmitters/METABOLISM
Rats
Rats, Sprague-Dawley
Thymectomy

PUBLICATION TYPES:
JOURNAL ARTICLE

Picamilon appears to be more effective than Hydergine or vinpocetin in improving blood flow to the cerebral vessels. Picamilon readily crosses the blood-brain barrier to protect neurons against the effects of diminished oxygen flow. It also produces cognitive-enhancing effects.

The combination of these effects provides an entirely new method of dealing safely with several causes of neurological aging. Picamilon is approved as a pharmaceutical product in Russia, but is really a vitamin-like compound consisting of a niacin analog (n-nicotinoyl) uniquely bonded to GABA (gamma aminobutyric acid). When niacin is bound to GABA, it creates a molecule that readily penetrates the blood-brain barrier to enhance cerebral and peripheral circulation. What enables picamilon to work so well is the synergism between the niacin and GABA molecules.

Suggested dose: One tablet, two to three times a day.
If cognitive enhancing results do not occur in 30 days, double the dose.

PIRACETAM

Piracetam is a derivative of the amino acid GABA that increases the sensitivity of receptors in the brain involved in memory and learning. Piracetam is called a nootropic drug because of its ability to enhance the mind. Studies in both animals and humans have demonstrated that Piracetam can improve memory, increase attention and cognition, improve spatial learning, and enhance motor mechanisms. Piracetam is one of the most popular "smart drugs" that is used to increase intelligence, information processing ability, concentration, memory, and creativity. It has been shown to harmonize and synchronize the spheres of the brain by anchoring information within the brain.

Suggested dose: Piracetam should be used in doses ranging from 1600 to 2400 mg a day taken first thing in the morning.

RETIN A

Retin A is a highly publicized vitamin A derivative that stimulates skin cell renewal, increasing the creation of youthful cells at the skin's surface. Retin A may produce side effects such as minor irritation. People using Retin A should stay out of the sun and use a sunblock for normal sunlight exposure, because Retin A increases skin sensitivity to sunlight.

A. INGREDIENT NAME:

QUINACRINE HYDROCHLORIDE

B. Chemical Name:

3-Chloro-7-methoxy-9-(1-methyl-4-diethylaminobutylamino)acridine Dihydrochloride; Mepacrine Hydrochloride; Quinacrinium Chloride
2-Chloro-5-(Omega-Diethylamino-Alpha-Methylbutylamino)-7-Methoxyacridine Dihydrochloride
3-Chloro-9-(4'-Diethylamino-1'-Methylbutylamino)-7-Methoxyacridine Dihydrochloride
6-Chloro-9-((4-(Diethylamino)-1-Methylbutyl)Amino)-2-Methoxyacridine Dihydrochloride
3-Chloro-7-Methoxy-9-(1-Methyl-4-Diethylaminobutylamino)Acridine Dihydrochloride
2-Methoxy-6-Chloro-9-(4-Diethylamino-1-Methylbutylamino)

C. Common Name:

Acrichine, Acriquine, Akrichin (Czech), Arichin, Atabrine, Atabrine Dihydrochloride, Atabrine Hydrochloride, Atebrin, Atebrine, AtebrinHydrochloride, Chemiochin, Chinacrin, Chinacrin Hydrochloride, Crinodora, Dial, Erion, Italchin, malaricida, Mecryl, Mepacrine Dihydrochloride, Mepacrine Hydrochloride, Methoquine, Acridine Dihydrochloride, Metochin, Metoquin, Metoquine, Palacrin, Palusan, Pentilen, Quinacrine Dihydrochloride, Quinacrine Hydrochloride

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

Assay: 100.12%
98 %

E. Information about how the ingredient is supplied:

Bright Yellow, Crystalline Powder. It is odorless and has a bitter taste.

F. Information about recognition of the substance in foreign pharmacopeias:

Pharmacopeias. In Arg., Belg., Br., Braz., Eur., Fr., Ger., Hung., Ind., It., Mex., Neth., Nord., Pol., Rus., Span., Swiss., Turk., and U. S.

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

H. Information about dosage forms used:

Tablets

I. Information about strength:

100mg - 900mg

J. Information about route of administration:

Orally

K. Stability data:

Melting Point: 257 C (DEC)
Incompatible with alkalis, nitrates, and oxidizing agents.

L. Formulations:

M. Miscellaneous Information:

CERTIFICATE OF ANALYSIS

The Drugs & Cosmetics Act 1940 and the rules thereunder

From 39 Rule 150 E (f)

Certificate No. VCL/ 17/97-98.

30-2193
53219

1. Name of the manufacturer : M/s. Vipor Chemicals, Baroda-390 010.
2. Licence No. : G/152
3. Date of Receipt : 03-07-97.
4. Name of Sample : MEPACRINE HYDROCHLORIDE B.P.
5.

(a) Batch No.	(b) Quantity Submitted	(c) Total Quantity Mfgd/Purchased	(d) Date of Manufacture	(e) Date of Expiry
025	2x 15gm.	-	JULY'97	JUNE'2002

6. RESULTS OF ANALYSIS — As per B.P.

Description	: Yellow Crystalline Powder
Solubility	: Comply
Identification	: A, B, C, D Comply
Acidity	: pH of 2% Solution : 4.0
3-Chloro -7-Methoxy Acridine	: Complies
Water	: 006.8 %
Sulphated Ash	: 000.07%
Assay	: 100.12%

9/97

Report : In the opinion of the undersigned, the sample referred to above is of STANDARD QUALITY/ is ~~NOT OF STANDARD QUALITY~~ as defined in the Act and the rules made thereunder.

The opinion is in respect of the tests carried out and mentioned above.

QUALITY CONTROL REPORT

CHEMICAL NAME.: QUINACRINE HYDROCHLORIDE USP

MANUFACTURE LOT NO.: 025

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP__/BP__/MERCK__/NF__/MART.__/CO.SPECS.__.

1) DESCRIPTION.:
BRIGHT YELLOW, CRYSTALLINE POWDER. IS ODORLESS AND HAS A BITTER TASTE.

2) SOLUBILITY.:
SPARINGLY SOLUBLE IN WATER; SOLUBLE IN ALCOHOL.

3) MELTING POINT.:
MELTS AT ABOUT 250 DEGREES WITH DECOMPOSITION.

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:
A) COMPLIES (A) AS PER IR SPECTRUM USP XXII.
B) COMPLIES (C) AS PER USP XXII.
C) A SOLUTION 1 IN 100 HAS A PH ABOUT 4.5.

PASSES.: _____ **FAILS.:** _____

COMMENTS.: QUINACRINE DIHYDROCHLORIDE IS ALSO KNOWN AS QUINACRINE HCL.

ANALYST SIGNATURE.: _____ **DATE.:** _____

PREPACK TEST.: _____ **DATE.:** _____ **INITIAL.:** _____

RETEST.: _____ **DATE.:** _____ **INITIAL.:** _____

---------- IDENTIFICATION ----------

PRODUCT #: 22299-2 NAME: QUINACRINE DIHYDROCHLORIDE HYDRATE, 98%

CAS #: 69-05-6

MF: C23H30CLN3O

SYNONYMS

ACRICHINE * ACRIQUINE * AKRICHIN (CZECH) * ARICHIN * ATABRINE * ATABRINE DIHYDROCHLORIDE * ATABRINE HYDROCHLORIDE * ATEBRIN * ATEBRINE * ATEBRIN HYDROCHLORIDE * CHEMIOCHIN * CHINACRIN * CHINACRIN HYDROCHLORIDE * (2-CHLORO-5-(OMEGA-DIETHYLAMINO-ALPHA-METHYLBUTYLAMINO) -7-METHOXYACRIDINE DIHYDROCHLORIDE * 3-CHLORO-9-(4'-DIETHYLAMINO-1'-METHYLBUTYLAMINO)-7-METHOXYACRIDINE DIHYDROCHLORIDE * 6-CHLORO-9-((4-(DIETHYLAMINO)-1-METHYLBUTYL)AMINO)-2-METHOXYACRIDINE DIHYDROCHLORIDE * 3-CHLORO-7-METHOXY-9-(1-METHYL-4-DIETHYLAMINOBUTYLAMINO)ACRIDINE DIHYDROCHLORIDE * CRINODORA * DIAL * ERION * ITALCHIN * MALARICIDA * MECRYL * MEPACRINE DIHYDROCHLORIDE * MEPACRINE HYDROCHLORIDE * METHOQUINE * 2-METHOXY-6-CHLORO-9-(4-DIETHYLAMINO-1-METHYLBUTYLAMINO) ACRIDINE DIHYDROCHLORIDE * METOCHIN * METOQUIN * METOQUINE * PALACRIN * PALUSAN * PENTILEN * QUINACRINE DIHYDROCHLORIDE * QUINACRINE HYDROCHLORIDE * 866 R.P. * SN 390 *

---------- TOXICITY HAZARDS ----------

RTECS NO: AR7875000

ACRIDINE, 6-CHLORO-9-((4-(DIETHYLAMINO)-1-METHYLBUTYL)AMINO)-2-METHOXY-, DIHYDROCHLORIDE

TOXICITY DATA

ORL-RAT LD50:660 MG/KG	JPETAB 91,157,47
IVN-RAT LD50:29 MG/KG	JPETAB 91,157,47
IUT-RAT LD50:100 MG/KG	IJEBA6 16,1074,78
ORL-MUS LD50:557 MG/KG	JPETAB 91,157,47
IPR-MUS LD50:189 MG/KG	JPETAB 91,133,47
SCU-MUS LD50:212 MG/KG	ABEMAV 1,317,41

IVN-MUS LD50:38 MG/KG JPETAB 91,157,47
ORL-RBT LD50:433 MG/KG JPETAB 91,157,47
IVN-RBT LD50:9 MG/KG JPETAB 91,157,47
IVN-GPG LD50:14 MG/KG JPETAB 91,157,47

REVIEWS, STANDARDS, AND REGULATIONS

NOES 1983: HZD X4102; NIS 1; TNF 66; NOS 3; TNE 987; TFE 508

EPA GENETOX PROGRAM 1988, NEGATIVE: SPERM MORPHOLOGY-MOUSE

EPA GENETOX PROGRAM 1988, INCONCLUSIVE: MAMMALIAN MICRONUCLEUS

TARGET ORGAN DATA

PERIPHERAL NERVE AND SENSATION (FLACCID PARALYSIS WITHOUT ANESTHESIA)
BEHAVIORAL (ALTERED SLEEP TIME)
BEHAVIORAL (SOMNOLENCE)
BEHAVIORAL (TOXIC PSYCHOSIS)
BEHAVIORAL (CONVULSIONS OR EFFECT ON SEIZURE THRESHOLD)
VASCULAR (OTHER CHANGES)
LUNGS, THORAX OR RESPIRATION (RESPIRATORY DEPRESSION)
LUNGS, THORAX OR RESPIRATION (OTHER CHANGES)
IMMUNOLOGICAL INCLUDING ALLERGIC (ANAPHYLAXIS)
PATERNAL EFFECTS (SPERMATOGENESIS)
MATERNAL EFFECTS (OVARIES, FALLOPIAN TUBES)
MATERNAL EFFECTS (UTERUS, CERVIX, VAGINA)
MATERNAL EFFECTS (MENSTRUAL CYLCE CHANGES OR DISORDERS)
MATERNAL EFFECTS (OTHER EFFECTS ON FEMALE)
EFFECTS ON FERTILITY (FEMALE FERTILITY INDEX)
EFFECTS ON FERTILITY (PRE-IMPLANTATION MORTALITY)
EFFECTS ON FERTILITY (POST-IMPLANTATION MORTALITY)
ONLY SELECTED REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES (RTECS)
DATA IS PRESENTED HERE. SEE ACTUAL ENTRY IN RTECS FOR COMPLETE INFORMATION.

---------- HEALTH HAZARD DATA ----------

ACUTE EFFECTS

HARMFUL IF SWALLOWED, INHALED, OR ABSORBED THROUGH SKIN.
MAY CAUSE EYE IRRITATION.
MAY CAUSE SKIN IRRITATION.
TO THE BEST OF OUR KNOWLEDGE, THE CHEMICAL, PHYSICAL, AND TOXICOLOGICAL PROPERTIES HAVE NOT BEEN THOROUGHLY INVESTIGATED.

FIRST AID

IN CASE OF CONTACT, IMMEDIATELY FLUSH EYES WITH COPIOUS AMOUNTS OF
WATER FOR AT LEAST 15 MINUTES.

IN CASE OF CONTACT, IMMEDIATELY WASH SKIN WITH SOAP AND COPIOUS

AMOUNTS OF WATER.
IF INHALED, REMOVE TO FRESH AIR. IF NOT BREATHING GIVE ARTIFICIAL RESPIRATION. IF BREATHING IS DIFFICULT, GIVE OXYGEN.
IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS CONSCIOUS.
CALL A PHYSICIAN.
WASH CONTAMINATED CLOTHING BEFORE REUSE.

---------- PHYSICAL DATA ----------

MELTING PT: 257 C (DEC)

APPEARANCE AND ODOR
YELLOW POWDER

---------- FIRE AND EXPLOSION HAZARD DATA ----------

EXTINGUISHING MEDIA
WATER SPRAY.
CARBON DIOXIDE, DRY CHEMICAL POWDER OR APPROPRIATE FOAM.

SPECIAL FIREFIGHTING PROCEDURES
WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING TO
PREVENT CONTACT WITH SKIN AND EYES.

UNUSUAL FIRE AND EXPLOSIONS HAZARDS
EMITS TOXIC FUMES UNDER FIRE CONDITIONS.

---------- REACTIVITY DATA ----------

INCOMPATIBILITIES
STRONG OXIDIZING AGENTS
STRONG ACIDS
MAY DISCOLOR ON EXPOSURE TO LIGHT.

HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS
TOXIC FUMES OF:
CARBON MONOXIDE, CARBON DIOXIDE
NITROGEN OXIDES
HYDROGEN CHLORIDE GAS

---------- SPILL OR LEAK PROCEDURES ----------

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED
EVACUATE AREA.
WEAR SELF-CONTAINED BREATHING APPARATUS, RUBBER BOOTS AND HEAVY

RUBBER GLOVES.
SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL.
AVOID RAISING DUST.
VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS COMPLETE.

WASTE DISPOSAL METHOD
DISSOLVE OR MIX THE MATERIAL WITH A COMBUSTIBLE SOLVENT AND BURN

IN A
CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER.

OBSERVE ALL FEDERAL, STATE, AND LOCAL LAWS.

--- PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE ---

CHEMICAL SAFETY GOGGLES.
RUBBER GLOVES.
NIOSH/MSHA-APPROVED RESPIRATOR.
SAFETY SHOWER AND EYE BATH.
USE ONLY IN A CHEMICAL FUME HOOD.
DO NOT BREATHE DUST.
DO NOT GET IN EYES, ON SKIN, ON CLOTHING.
WASH THOROUGHLY AFTER HANDLING.
TOXIC.
KEEP TIGHTLY CLOSED.
LIGHT SENSITIVE
STORE IN A COOL DRY PLACE.
HARMFUL BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.

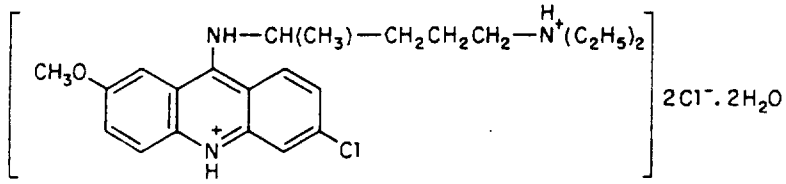
WEAR SUITABLE PROTECTIVE CLOTHING.

Packaging and storage—Preserve Pyroxylin loosely packed in cartons, protected from light.

CATEGORY—Pharmaceutic necessity for COLLODION.

QUINACRINE HYDROCHLORIDE

3-Chloro-7-methoxy-9-(1-methyl-4-diethylaminobutylamino)acridine Dihydrochloride; Mepacrine Hydrochloride; Quinacrinium Chloride



$C_{23}H_{30}ClN_3O.2HCl.2H_2O$ Mol. wt. 508.94

Quinacrine Hydrochloride contains not less than 98 per cent of $C_{23}H_{30}ClN_3O.2HCl.2H_2O$.

Description—Quinacrine Hydrochloride occurs as a bright yellow, crystalline powder. It is odorless and has a bitter taste.

Solubility—One Gm. of Quinacrine Hydrochloride dissolves in about 35 ml. of water. It is soluble in alcohol.

Identification—

A: To 5 ml. of a solution of Quinacrine Hydrochloride (1 in 40), add a slight excess of ammonia T.S.: a yellow to orange, oily precipitate of quinacrine base is formed which adheres to the wall of the vessel and is soluble in ether.

B: To 5 ml. of a solution of Quinacrine Hydrochloride (1 in 40), add 1 ml. of diluted nitric acid: a yellow crystalline precipitate is formed.

C: To 5 ml. of a solution of Quinacrine Hydrochloride (1 in 40), add 1 ml. of mercuric chloride T.S.: a yellow precipitate is formed.

D: The filtrate from the precipitate, obtained in *Identification test A*, acidified with nitric acid, responds to the tests for *Chloride*, page 901.

pH—The pH of a solution of Quinacrine Hydrochloride (1 in 100) is about 4.5.

Water, page 942—Determine the water content of Quinacrine Hydrochloride by drying at 105° for 4 hours or by the Karl Fischer method: it contains not less than 6 per cent and not more than 8 per cent of water.

Residue on ignition, page 912—The residue on ignition of 200 mg. of Quinacrine Hydrochloride is negligible.

Assay—Transfer to a 100-ml. volumetric flask about 250 mg. of Quinacrine Hydrochloride, accurately weighed, dissolve it in 10 ml. of water, then add 10 ml. of a solution prepared by dissolving 25 Gm. of sodium acetate and 10 ml. of glacial acetic acid in water to make 100 ml. Add exactly 50 ml. of 0.1 *N* potassium dichromate and water to make 100 ml., stopper the flask, mix thoroughly, and filter through a dry filter paper into a dry flask, rejecting the first 15 ml. of the filtrate. Measure 50 ml. of the subsequent filtrate into a glass-stoppered flask, add 15 ml. of hydrochloric acid and 20 ml. of potassium iodide T.S., stopper the flask, mix the contents gently, and allow to stand in the dark for 5 minutes. Add 75 ml. of water, and titrate the liberated iodine with 0.1 *N* sodium thiosulfate, adding starch T.S. as the end-point is neared. Perform a blank determination with the same quanti-

ties of the same reagents and in the same manner (see *Residual Titrations*, page 832). Each ml. of 0.1 *N* potassium dichromate is equivalent to 8.482 mg. of $C_{23}H_{30}ClN_3O.2HCl.2H_2O$.

Packaging and storage—Preserve Quinacrine Hydrochloride in tight, light-resistant containers.

CATEGORY—Anthelmintic; antimalarial; antiprotozoan.

DOSE—USUAL—Suppressive—

Antimalarial—100 mg.

Therapeutic—

Antimalarial and antiprotozoan—200 mg. every 6 hours for 5 doses, then 100 mg. three times a day for 6 days.

Anthelmintic—500 mg. with 500 mg. of sodium bicarbonate in a single dose.

Quinacrine Hydrochloride Tablets

QUINACRINE HYDROCHLORIDE TABLETS

Quinacrine Hydrochloride Tablets contain not less than 93 per cent and not more than 107 per cent of the labeled amount of $C_{23}H_{30}ClN_3O.2HCl.2H_2O$.

Identification—

A: Powder a sufficient number of Quinacrine Hydrochloride Tablets, equivalent to about 250 mg. of quinacrine hydrochloride, and extract with two 15-ml. portions of hot water, filtering after each extraction. To 5 ml. of the extract add ammonia T.S., and remove the oily precipitate so formed by extraction with two 10-ml. portions of ether. The water layer, acidified with nitric acid, responds to the tests for *Chloride*, page 901.

B: To the remaining portion of the water extract obtained in *Identification test A* add 2 ml. of ammonia T.S.: a yellow, oily precipitate forms. Shake the mixture with several 10-ml. portions of chloroform until the water layer is practically colorless. Evaporate the combined chloroform solutions on a steam bath in a small beaker, and add to the residue 3 ml. of hot water and 2 ml. of diluted hydrochloric acid, moistening the sides of the beaker with the liquid and stirring with a glass rod. Allow to stand for 30 minutes, then filter, wash the crystals with ice-cold water until the last washing is practically neutral to litmus, and dry at 105° for 2 hours: the crystals so obtained respond to *Identification tests B* and *C* under *Quinacrine Hydrochloride*, page 599.

Disintegration—Quinacrine Hydrochloride Tablets meet the requirements of the *Disintegration Test for Tablets*, page 936, in not more than 1 hour.

Weight variation—Quinacrine Hydrochloride Tablets meet the requirements of the *Weight Variation Test for Tablets*, page 945.

Assay—Weigh a counted number of not less than 20 Quinacrine Hydrochloride Tablets, and reduce them to a fine powder without appreciable loss. Weigh accurately a portion of the powder, equivalent to about 200 mg. of quinacrine hydrochloride, and place it in a separator with 25 ml. of water and 3 ml. of diluted hydrochloric acid. Extract the suspension with two 15-ml. portions of chloroform, and wash the chloroform extracts in a second separator with 10 ml. of water. Discard the washed chloroform, and add the water in the second separator to the suspension of tablet

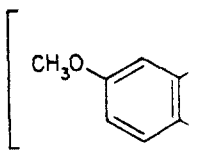
material. Make the s
pletely with successive
extract is colorless. I
cotton moistened with
form. Gently evapora
15 minutes. To the resi
steam bath until the q
pletely with the aid of 2
proceed as directed in t
ning with "then add 10 r
is equivalent to 8.482 n

Packaging and storage—
tainers.

Tablets available—Quina
following amounts of qu

CATEGORY and Dos

Q



$(C_{20}H_{24}N_2O_2)_2.H_2SO_4$.

Quinidine Sulfate is
species of *Cinchona* a
Flückiger (Fam. *Rubi*

Description—Quinidine S
cohering in masses. It
to light. Its solutions a

Solubility—One Gm. of
about 10 ml. of alcohol.

Identification—

A: Acidify a solution
ing solution has

B: To 5 ml. of a solut
mine T.S., and t
green color due

C: To 5 ml. of a soluti
T.S., and stir wi
interval (distinct

D: Quinidine Sulfate

Specific rotation, page 80
the anhydrous basis, d
Quinidine Sulfate in ea

1378-w

quine. Cyclochin; Haloquine. 4-(7-Chloro-4-amino)-2,6-bis(dihexylaminomethyl)phenol.
$C_{...}ClN_4O$ = 497.1.

CAS — 14594-33-3.

A yellow crystalline powder with a bitter taste. Practically **insoluble** in water; readily soluble in dilute acids; insoluble in dilute alkalis. **Protect** from light.

Uses. Cycloquine resembles chloroquine in its action and has been used in the USSR for the suppression and treatment of malaria. A dose of 300 mg has been given weekly for the suppression of malaria and 300 mg has been given daily for three days in the treatment of acute attacks.

1379-e

Diformyldapsone. DFD; DFDDS; Diformyldiaminodiphenylsulphone. 4,4'-Sulphonylbisformanilide.
$C_{14}H_{12}N_2O_3S$ = 304.3.

CAS — 6784-25-4.

A crystalline solid. M.p. 267° to 269°. Practically **insoluble** in water; soluble 1 in about 200 of dimethyl sulphoxide. It is most stable at pH 6.

Uses. Diformyldapsone has been used as an antimalarial in doses of 400 to 800 mg weekly, but is given with chloroquine, primaquine, or pyrimethamine, since it has no action on gametocytes.

Diformyldapsone had an approximate half-life of 84 hours.— W. Peters, *Postgrad. med. J.*, 1973, *49*, 573.

Diformyldapsone in doses of 3.2 g twice weekly for 4 weeks damaged the red blood cells in 25 subjects. Smaller doses did not appear to cause haemolysis.— S. A. Cucinell *et al.*, *J. clin. Pharmac.*, 1974, *14*, 51.

Malaria. Diformyldapsone was considered to protect volunteers more effectively against the Vietnam Smith strain of *P. falciparum* than against the Chesson strain of *P. vivax*. There were no reports of methaemoglobinaemia in patients receiving diformyldapsone alone in conjunction with chloroquine.— Clyde. D.F. *et al.*, *Milit. Med.*, 1971, *136*, 836, per *Trop. Dis. Bull.*, 1972, *69*, 593. See also *idem*, *Milit. Med.*, 1970, *135*, 527.

Diformyldapsone 100 to 800 mg weekly given with chloroquine alone, or with chloroquine and primaquine, suppressed the Smith strain of falciparum malaria in 41 of 45 men and the Brai. strain in 9 men. The combination appeared to be more effective than treatment with chloroquine and primaquine, or than pyrimethamine 25 mg weekly which suppressed the Brai. but not the Smith strain.— D. F. Clyde *et al.*, *Am. J. trop. Med. Hyg.*, 1971, *20*, 1, per *Trop. Dis. Bull.*, 1971, *68*, 1153.

Diformyldapsone given weekly with chloroquine protected 5 of 8 volunteers against falciparum malaria. Better results were noted when volunteers were given dapsone daily with chloroquine or chloroquine and primaquine weekly.— D. Willerson, *Am. J. trop. Med. Hyg.*, 1972, *21*, 138, per *J. Am. med. Ass.*, 1972, *220*, 1382.

Diformyldapsone, 400 to 800 mg with pyrimethamine 25 mg, both given weekly, was considered to provide effective prophylaxis against chloroquine-resistant *P. falciparum* and against *P. vivax*. No toxic side-effects were noted.— D. F. Clyde *et al.*, *Milit. Med.*, 1973, *138*, 418, per *Trop. Dis. Bull.*, 1974, *71*, 15.

1380-b

Hydroxychloroquine Sulphate *(B.P.)*

Hydroxychloroquine Sulfate *(U.S.P.)*; Oxichlorochin Sulphate; Win 1258-2. 2-{*N*-[4-(7-Chloro-4-quinolylamino)pentyl]-*N*-ethylamino}ethanol sulphate.
$C_{18}H_{26}ClN_3O, H_2SO_4$ = 433.9.

CAS — 118-42-3 (hydroxychloroquine); 747-36-4 (sulphate).

Ph ... poeias. In *Br.* and *U.S.*

A white or almost white odourless crystalline powder with a bitter taste. There are 2 forms, one melting at about 198° and the other at about 240°. Hydroxychloroquine sulphate 100 mg is approximately equivalent to 77 mg of hydroxychloroquine base. **Soluble** 1 in 5 of water; practically insoluble in alcohol, chloroform, and ether. A 1% solution in water has a pH of 3.5 to 5.5. **Protect** from light.

Adverse Effects, Treatment, Precautions, and Resistance. As for Chloroquine, p.395.

Hydroxychloroquine was given in an average dose of 800 mg daily for up to 4½ years to 94 patients with lupus erythematosus, rheumatoid arthritis, or scleroderma. The patients had not previously received chloroquine, amodiaquine, mepacrine, or quinine. Corneal deposition occurred in 26 patients; it was reversible in 20, persistent in 3, and 3 were lost to follow-up. There was a rapid rise in incidence after 150 g had been given. One patient who had received 770 g over 26½ months developed retinopathy. A second case of probable retinopathy was subsequently seen in a further patient.— R. V. Shearer and E. L. Dubois, *Am. J. Ophthal.*, 1967, *64*, 245.

Ocular toxicity in 3 of 99 patients after long-term treatment with hydroxychloroquine.— R. I. Rynes *et al.*, *Arthritis Rheum.*, 1979, *22*, 832.

Uses. Hydroxychloroquine sulphate has an antimalarial action similar to that of chloroquine (see p.396) but it is mainly used in the treatment of systemic and discoid lupus erythematosus and rheumatoid arthritis. Treatment is usually started with about 400 to 800 mg daily in divided doses with meals and the dose is reduced to about 200 to 400 mg when a response occurs. In malaria, a suppressive dose of 400 mg every 7 days is used, and in treating an acute attack a dose of 800 mg has been used, followed after 6 to 8 hours by 400 mg and a further 400 mg on each of the 2 following days. Children may be given a weekly suppressive dose equivalent to 5 mg of base per kg body-weight, while for treatment an initial dose of 10 mg per kg may be given, following by 5 mg per kg 6 hours later and again on the second and third days.

In the treatment of giardiasis, the usual dose is 200 mg thrice daily for 5 days.

Hydroxychloroquine sulphate has been used in the treatment of polymorphous light eruptions. The dose is as for rheumatoid arthritis.

Porphyria. Hydroxychloroquine, 400 mg weekly for several months, had been reported to be safe and effective in the treatment of porphyria cutanea tarda.— F. De Matteis, *Br. J. Derm.*, 1972, *87*, 174.

Thrombo-embolic disorders. Of 565 patients who underwent surgery 284 received an injection of hydroxychloroquine sulphate 200 mg with their premedication and then 200 mg eight-hourly by mouth or by injection until discharge from hospital. From postoperative observations and by phlebography it appeared that hydroxychloroquine could be useful in reducing the incidence of deep-vein thrombosis and pulmonary embolism.— A. E. Carter *et al.*, *Br. med. J.*, 1971, *1*, 312.

The incidence of deep-vein thrombosis after surgery was 5% in 107 patients given hydroxychloroquine sulphate compared with 16% in 97 controls. The dose was 1.2 g by mouth in 3 divided doses in the 24 hours before surgery followed by 400 mg every 12 hours after surgery until discharge.— A. E. Carter and R. Eban, *Br. med. J.*, 1974, *3*, 94.

For discussions, see A. S. Gallus and J. Hirsh, *Drugs*, 1976, *12*, 132; A. G. G. Turpie and J. Hirsh, *Br. med. Bull.*, 1978, *34*, 183.

Preparations

Hydroxychloroquine Sulfate Tablets *(U.S.P.)*. Tablets containing hydroxychloroquine sulphate.

Hydroxychloroquine Tablets *(B.P.)*. Tablets containing hydroxychloroquine sulphate. They are sugar-coated.

Plaquenil *(Winthrop, UK)*. Hydroxychloroquine sulphate, available as tablets of 200 mg. (Also available as Plaquenil in *Aust., Austral., Belg., Canad., Denm., Fin., Fr., Iceland, Ital., Neth., Norw., Swed., Switz., USA*).

Other Proprietary Names

Ercoquin *(Denm., Norw., Swed.)*; Quensyl *(Ger.)*.

1381-v

Mefloquine Hydrochloride. WR 142490.

(±)-α-[2,8-Bis(trifluoromethyl)-4-quinolyl]-α-(2-piperidyl)methanol hydrochloride.
$C_{17}H_{16}F_6N_2O, HCl$ = 414.8.

CAS — 53230-10-7 (mefloquine); 51773-92-3 (hydrochloride).

Adverse Effects. Epigastric discomfort has been reported after doses of 1 g, and nausea and dizziness after doses of 1.75 or 2 g.

Uses. Mefloquine hydrochloride is a 4-quinolinemethanol compound which has schizonticidal activity against malaria parasites. It is active against chloroquine-resistant falciparum malaria.

Malaria. A preliminary study in 17 subjects of the use of mefloquine hydrochloride in single 1-g doses as a prophylactic against drug-resistant malaria.— K. H. Rieckmann *et al.*, *Bull. Wld Hlth Org.*, 1974, *51*, 375.

Thirty-five non-immune volunteers infected with 1 of 3 strains of *Plasmodium falciparum*, 2 of them drug-resistant, were treated with a single oral dose of mefloquine hydrochloride 0.4, 1, or 1.5 g. The infection was cured in 2 of 12 given 0.4 g, 13 of 15 given 1 g, and 8 of 8 given 1.5 g. In 5 partially-immune volunteers infected with *P. vivax* cures were achieved with single doses of 0.4 or 1 g in two, but infection reappeared in the remaining 3 subjects and was subsequently cured with chloroquine and primaquine.— G. M. Trenholme *et al.*, *Science*, 1975, *190*, 792.

None of 21 volunteers bitten by 10 to 15 mosquitoes heavily infected with *P. falciparum* developed malaria when given mefloquine hydrochloride 250 or 500 mg weekly, 500 mg every 2 weeks, or 1 g every 4 weeks. Doses of 250 mg weekly suppressed *P. vivax* infections during drug administration but malaria appeared when treatment ceased.— D. F. Clyde *et al.*, *Antimicrob. Ag. Chemother.*, 1976, *9*, 384.

Of 39 patients with chloroquine-resistant falciparum **malaria**, 36 (92%) were cleared of infection with no recrudescence after treatment with quinine, sulfadoxine, and pyrimethamine, by the regimen of A.P. Hall (*Br. med. J.*, 1975, *2*, 15; see under Quinine, p.405), while all of 35 were cleared by treatment with quinine followed by a single dose of mefloquine hydrochloride 1.5 g (one patient received only 1 g). Side-effects in 40 patients given mefloquine were: abdominal pain (7), anorexia (6), diarrhoea (6), dizziness (9), nausea (3), vomiting (9), and weakness (3). Side-effects were minimal or absent if at least 12 hours elapsed after the last dose of quinine.— A. P. Hall *et al.*, *Br. med. J.*, 1977, *1*, 1626.

Animal studies of the antimalarial activities of 4-quinolinemethanols including mefloquine and a report of the US Army Malaria Research Program.— L. H. Schmidt *et al.*, *Antimicrob. Ag. Chemother.*, 1978, *13*, 1011.

Of 37 patients with chloroquine-resistant falciparum malaria all were radically cured by a single dose of mefloquine hydrochloride 1.5 g. Side-effects (nausea, vomiting, diarrhoea, dizziness, headache) could probably be reduced by a formulation designed to slow absorption.— E. B. Doberstyn *et al.*, *Bull. Wld Hlth Org.*, 1979, *57*, 275.

Metabolism. Preliminary study in 1 subject given a single dose of mefloquine indicated relatively rapid absorption, extensive distribution, and prolonged elimination phases. Mefloquine was reported to be extensively bound to plasma proteins and to be concentrated in erythrocytes.— J. M. Grindel *et al.*, *J. pharm. Sci.*, 1977, *66*, 834.

The kinetics of mefloquine hydrochloride.— R. E. Desjardins *et al.*, *Clin. Pharmac. Ther.*, 1979, *26*, 372.

1382-g

Mepacrine Hydrochloride *(B.P., Eur. P.)*

Mepacrini Hydrochloridum; Acrinamine; Quinacrine Hydrochloride *(U.S.P.)*; Quinacrinium Chloride; Acrichinum; Antimalarinae Chlorhydras; Chinacrina. 6-Chloro-9-(4-diethylamino-1-methylbutylamino)-2-methoxyacridine dihydrochloride dihydrate.
$C_{23}H_{30}ClN_3O, 2HCl, 2H_2O$ = 508.9.

CAS — 83-89-6 (mepacrine); 69-05-6 (dihydrochloride, anhydrous); 6151-30-0 (dihydrochloride, dihydrate).

Pharmacopoeias. In *Arg., Belg., Br., Braz., Eur., Fr., Ger., Hung., Ind., Int., It., Mex., Neth., Nord., Pol., Rus., Span., Swiss, Turk.*, and *U.S.*

A bright yellow odourless crystalline powder with a bitter taste. M.p. about 250° with decomposition. **Soluble** 1 in 35 to 40 of water; soluble in alcohol; slightly soluble in dehydrated alcohol; very slightly soluble in chloroform; practically insoluble in acetone and ether. A 2% solution in water has a pH of 3 to 5. **Incompatible** with alkalis, nitrates, and oxidising agents. **Store** in airtight containers. Protect from light.

Incompatibility. Mepacrine hydrochloride was incompatible with amaranth, benzylpenicillin, sodium alginate, sodium aminosalicylate, sodium carboxymethylcellulose, sodium lauryl sulphate, and thiomersal.— *J. Am. pharm. Ass., pract. Pharm. Edn*, 1952, *13*, 658.

Adverse Effects. Minor effects liable to arise with ordinary doses are dizziness, headache, and mild gastro-intestinal disturbances. Most patients develop a yellow discoloration of the skin. Large doses may give rise to nausea and vomiting and occasionally to transient mental disturbances. A few patients develop chronic dermatoses after prolonged administration of the drug; these may be either lichenoid, eczematoid, or exfoliative in type. Deaths from exfoliative dermatitis and from hepatitis have been reported. The use of mepacrine over prolonged periods may give rise to aplastic anaemia.

Adverse effects of intrapleural instillation include fever and chest pain caused by the inflammatory reaction.

The toxicity arising from prolonged administration has contributed to the decline in the use of mepacrine in malaria.

Two patients had convulsions a few hours after the intrapleural administration of mepacrine hydrochloride 400 mg for malignant effusions. One developed status epilepticus and died; the other was successfully controlled with phenobarbitone intravenously and phenytoin by mouth.— I. Borda and M. Krant, *J. Am. med. Ass.*, 1967, *201*, 1049.

Mepacrine hydrochloride 100 mg daily had been reported to cause haemolytic anaemia in certain individuals with a deficiency of glucose-6-phosphate dehydrogenase. The reaction was not considered clinically significant under normal circumstances (e.g. in the absence of infection).— E. Beutler, *Pharmac. Rev.*, 1969, *21*, 73.

A patient with rheumatoid arthritis treated with mepacrine hydrochloride for about 20 years had developed a blue-black discoloration of the hard palate, the nail beds, and the skin over the shins. The colour disappeared when mepacrine was stopped and reappeared when it was restarted.— M. J. Egorin *et al.*, *J. Am. med. Ass.*, 1976, *236*, 385.

Treatment of Adverse Effects. As for Chloroquine, p.396.

Precautions. Mepacrine enhances the toxicity of the 8-aminoquinoline derivatives such as primaquine by inhibiting their metabolism.

Mepacrine might interfere with fluorimetric estimations of plasma hydrocortisone.— J. Millhouse, *Adverse Drug React. Bull.*, 1974, Dec., 164.

Absorption and Fate. Mepacrine is absorbed from the gastro-intestinal tract and appears in the blood within 2 hours. It becomes concentrated in liver, pancreas, spleen, and lung, and higher concentrations occur in red and white blood cells than in plasma, but it also permeates into all body fluids and crosses the placenta. It has a biological half-life of about 5 days and is excreted only very slowly in the urine and faeces.

Mepacrine hydrochloride was bound to serum proteins *in vitro*.— G. A. Lutty, *Toxic. appl. Pharmac.*, 1978, *44*, 225.

Uses. Mepacrine was formerly widely used for the suppression and treatment of malaria but it has been superseded for these purposes by chloroquine and other more recently introduced antimalarials. Doses ranged from 100 mg daily for suppression and from 900 mg reducing to 300 mg daily for treatment. Mepacrine hydrochloride is used in the treatment of giardiasis; 100 mg thrice daily for 7 days is usually effective, though relapses may occur. A suggested dose for children is 2.7 mg per kg body-weight thrice daily.

It has been used for the expulsion of tapeworms; 100 mg is given at intervals of 5 minutes until a total dose of 1 g is reached.

Instillations of mepacrine hydrochloride or mesylate are used in the symptomatic treatment of neoplastic effusions in the pleura or peritoneum but the treatment is associated with a high frequency of toxic effects.

For the use of mepacrine as an anthelmintic, see A. Davis, *Drug Treatment in Intestinal Helminthiases*, Geneva, World Health Organization, 1973.

Giardiasis. Mepacrine 100 mg thrice daily for 5 to 7 days was usually effective in the treatment of giardiasis, although a second course might be required. The dose for children under 4 years old was one-quarter of the adult dose.— *Br. med. J.*, 1974, *2*, 347.

A 95% cure-rate was obtained in giardiasis after treatment with mepacrine hydrochloride 100 mg thrice daily for 7 days. Dosages in children were: under 1 year, 33 mg thrice daily; 1 to 4 years, 50 mg twice daily; 4 to 8 years, 50 mg thrice daily; over 8 years, 100 mg thrice daily, all for 7 days.— M. S. Wolfe, *J. Am. med. Ass.*, 1975, *233*, 1362.

Further references: G. T. Moore *et al.*, *New Engl. J. Med.*, 1969, *281*, 402; *Med. Lett.*, 1976, *18*, 39; R. E. Raizman, *Am. J. dig. Dis.*, 1976, *21*, 1070.

Malignant effusions. The value of local instillations of mepacrine in controlling effusions in advanced disseminated neoplastic disease was studied in 60 patients. For pleural effusions, an initial dose of 50 to 100 mg was followed by 200 to 400 mg daily for 4 or 5 days; patients with ascites received 100 to 200 mg followed by 400 to 800 mg daily for 3 to 5 days. The mepacrine was dissolved in 10 ml of the effusion fluid which was then re-injected. Of 33 patients clinically evaluated for 2 months or more, objective control of the effusion was maintained in 27 for 2 to 26 months. Fever, often accompanied by leucocytosis and persisting for a few hours to 10 days after completion of treatment, was noted in about half the patients.— J. E. Ultmann *et al.*, *Cancer*, 1963, *16*, 283.

Thirteen patients with neoplastic effusions were treated with mepacrine hydrochloride in doses of 100 to 200 mg daily by local instillations for pleural effusions, and 200 to 400 mg daily for ascites, usually for 3 to 5 days. Clinical benefit with favourable objective changes in all measurable criteria of the disease was seen in 9 patients for periods of up to 27 months. Mild local toxicity was frequent but haematopoietic depression did not occur. No consistent cytolytic changes of tumour cells were observed and response was attributed to the inflammation and fibrosis produced.— M. R. Dollinger *et al.*, *Ann. int. Med.*, 1967, *66*, 249.

There was a response in 8 of 12 patients with malignant pleural effusions given mepacrine by instillation in small daily doses, and in 19 of 27 given mepacrine as a single dose through a thoracostomy tube. More disturbing and serious toxicity occurred in the second group.— E. R. Borja and R. P. Pugh, *Cancer*, 1973, *31*, 899.

A beneficial effect (less than 500 ml fluid drawn at each pleurocentesis in 3 months) was achieved on 9 of 14 occasions after the instillation of mepacrine (100, 200, and 200 mg respectively on 3 occasions in 1 week), on 4 of 15 occasions after thiotepa (20 mg per instillation), and on 1 of 9 occasions after pleurocentesis alone. Fever and chest pain were limiting factors; mepacrine was suitable if the patient's condition and prognosis was good; otherwise thiotepa or pleurocentesis were preferred.— J. Mejer *et al.*, *Scand. J. resp. Dis.*, 1977, *58*, 319.

Further references: J. A. Hickman and M. C. Jones, *Thorax*, 1970, *25*, 226; M. Lee and D. A. Boyes, *J. Obstet. Gynaec. Br. Commonw.*, 1971, *78*, 843.

Pneumothorax. A patient with cystic fibrosis was treated for pneumothorax on the left side by the instillation of mepacrine hydrochloride 100 mg in 15 ml saline into the intrapleural space on 4 consecutive days. This procedure was repeated 12 months later for pneumothorax on the right. There was no recurrence of pneumothorax on either side before the patient died 11 months after the second treatment after several relapses of chronic pulmonary disease.— J. Kattwinkel *et al.*, *J. Am. med. Ass.*, 1973, *226*, 557. See also R. E. Jones and S. T. Giammona, *Am. J. Dis. Child.*, 1976, *130*, 777.

Tubal occlusion. Two to 4 ml of a 30% aqueous suspension of mepacrine hydrochloride instilled transvaginally once in the immediate postmenstrual phase of 2 consecutive cycles induced tubal occlusion in 93% of 134 women.— Advances in Methods of Fertility Regulation, *Tech. Rep. Ser. Wld Hlth Org. No. 527*, 1973.

Sixty women desiring sterilisation were treated by the application, by cannula within the uterus, of 1 g of mepacrine hydrochloride suspended in 7 ml of sterile water. Of 52 available for examination 4 months later, 22 had bilateral tubal patency and 3 unilateral patency, a further 6 were pregnant. The low success-rate of a single application indicated limited usefulness.— C. Israngkun *et al.*, *Contraception*, 1976, *14*, 75.

Warts. A local injection technique was used in the treatment of warts in children. A 4% solution of mepacrine, in doses of 0.1 to 0.2 ml, was injected into the healthy skin at the base of the wart, 3 to 6 warts being treated at each session. The injections were repeated twice if no response followed the first injection. The treatment was successful in 97 of 112 patients. It sometimes caused slight transient pain.— A. I. Lopatin, *Pediatriya*, 1966, *45*, 71, per *Abstr. Wld Med.*, 1966, *40*, 446.

Preparations

Mepacrine Tablets *(B.P.).* Tablets containing mepacrine hydrochloride. Protect from light.

Quinacrine Hydrochloride Tablets *(U.S.P.).* Tablets containing mepacrine hydrochloride. Store in airtight containers.

Proprietary Names

Atabrine *(Winthrop, Canad.)*; Atabrine Hydrochloride *(Winthrop, USA)*.

Mepacrine hydrochloride was formerly marketed in certain countries under the proprietary name Quinacrine (*May & Baker*).

1383-q

Mepacrine Mesylate. Mepacrine Methanesulphonate *(B.P.C. 1963).*

$C_{23}H_{30}ClN_3O,2CH_3SO_3H,H_2O = 610.2$.

CAS — 316-05-2 (anhydrous).

Bright yellow odourless crystals with a bitter taste. Mepacrine mesylate 120 mg is approximately equivalent to 100 mg of mepacrine hydrochloride. **Soluble** 1 in 3 of water and 1 in 36 of alcohol. A 2% solution in water has a pH of 3 to 5. **Protect** from light. Solutions should not be heated, or stored for any length of time.

Uses. Mepacrine mesylate has actions similar to those of mepacrine hydrochloride, but as it is more soluble than the hydrochloride it has been administered by intramuscular injection in the treatment of severe malaria. A dose of 360 mg has been given in 2 to 4 ml of Water for Injections.

It is given by intrapleural or intraperitoneal instillation in the treatment of neoplastic effusions.

Preparations

Mepacrine Methanesulphonate Injection *(B.P.C. 1963).* Mepacrine Mesylate Injection. A sterile solution of mepacrine mesylate in Water for Injections, prepared by dissolving, immediately before use, the sterile contents of a sealed container in Water for Injections.

Mepacrine mesylate was formerly marketed in certain countries under the proprietary name Quinacrine Soluble (*May & Baker*).

1384-p

Pamaquin *(B.P. 1953).* Gametocidum; Pamachin; Pamaquine Embonate; Plasmoquinum; SN 971. 8-(4-Diethylamino-1-methylbutylamino)-6-methoxyquinoline 4,4'-methylenebis(3-hydroxy-2-naphthoate).

$C_{42}H_{45}N_3O_7 = 703.8$.

CAS — 491-92-9 (base); 635-05-2 (embonate).

A yellow to orange-yellow odourless powder with a bitter taste. Practically **insoluble** in water; soluble 1 in 20 of alcohol.

Uses. Pamaquin was formerly used in the treatment of malaria but has been superseded by primaquine phosphate.

A. INGREDIENT NAME:

SILVER PROTEIN MILD NF

B. Chemical Name:

C. Common Name:

Argentum Crede, Collargol (9CI), Colloidal Silver, Stillargol, Vitargénol, Aust.: Coldargan, Fr.: Pastaba, Ger.: Coldargan, Ital.: Arscolloid, Bio-Arscolloid, Corti-Ascolloid, Rikosilver, Rinatipiol, Rinovit Nube.

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

	(Specifications)	*(Results)*
Assay: (after ignition)	19.0-23.0%	19.74%

E. Information about how the ingredient is supplied:

Brown, Dark-Brown,or almost black, odorless, lustrous scales or granules, somewhat hygroscopic, and is affected by light.

F. Information about recognition of the substance in foreign pharmacopeias:

Aust., Belg., Cz., Fr., Hung., It., and Jpn.

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Isenberg, S., Apt, L., and Yoshimuri. Chemical preparation of the eye in ophthalmic surgery. II. Effectiveness of mild silver protein solution. *Archives of Opthalmology,* 1983; 101(5): 764-765.

Apt, L. and Isenberg, S. Chemical preparation of skin and eye in ophthalmic surgery: an international survey. *Opthalmic Surgery,* 1982; 13(12): 1026-1029.

H. Information about dosage forms used:

Liquid

I. Information about strength:

1-20%

J. Information about route of administration:

Nasal
Opthalmic

K. Stability data:

L. Formulations:

M. Miscellaneous Information:

30-1263
51149

CERTIFICATE OF ANALYSIS

PRODUCT: SILVER PROTEIN MILD
RELEASE #: N

LOT # :B61695G18

GRADE:NFXIII
CODE:D5785

		SPECIFICATIONS	RESULT
1.	DESCRIPTION	Black granules	Conforms
2.	Identification	To pass test	Passes test
3.	Solubility	To pass test	Passes test
4.	Assay (after ignition) D	19.0 - 23.0%	19.74%
5.	Ionic silver	No turbidity	Conforms
6.	Distinction from strong silver protein	To pass test	Passes test

ATTENTION: TONY HATCHETT

Date :06/23/97

Prepared by : A. HAZARI

10762

Approved by 6/97

QUALITY CONTROL REPORT

CHEMICAL NAME.: SILVER PROTEIN MILD NF A

MANUFACTURE LOT NO.: C64051D10

PHYSICAL TEST

SPECIFICATION TEST STANDARD.:USP__/BP__/MERCK__/NF__/MART.__/CO.SPECS.__.

1)DESCRIPTION.:
E BROWN,DARK-BROWN,OR ALMOST BLACK,ODORLESS,LUSTROUS SCALES OR GRANULES; SOMEWHAT HYGROSCOPIC,AND IS AFFECTED BY LIGHT.

2)SOLUBILITY.:
FREELY SOLUBLE IN WATER. ALMOST INSOLUBLE IN ALCOHOL,CHLOROFORM AND IN ETHER.

3)MELTING POINT.:

4)SPECIFIC GRAVITY .:

5)IDENTIFICATION.:
A)COMPLIES (B) AS PER NF 10th EDITION 1955.
B)COMPLIES (C) AS PER NF 10th EDITION 1955.

PASSES.:_____ **FAILS.:**_____

COMMENTS.:

ANALYST SIGNATURE.:_____ **DATE.:**_____

PREPACK TEST.:_____ **DATE.:**_____ **INITIAL.:**_____

RETEST.:_____ **DATE.:**_____ **INITIAL.:**_____

---------- IDENTIFICATION ----------

PRODUCT #: 29824-7 NAME: SILVER PROTEIN, MILD

CAS #: 9015-51-4

SYNONYMS

ARGENTUM CREDE * COLLARGOL (9CI) * COLLOIDAL SILVER *

---------- TOXICITY HAZARDS ----------

RTECS NO: VW3675000

SILVER, COLLOIDAL

TOXICITY DATA

ORL-MUS LD50:100 MG/KG JPPMAB 2,20,50

REVIEWS, STANDARDS, AND REGULATIONS

ACGIH TLV-TWA 0.01 MG(AG)/M3 85INA8 5,529,86

MSHA STANDARD-AIR:TWA 0.01 MG(AG)/M3 DTLVS* 3,231,71

ONLY SELECTED REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES (RTECS)

DATA IS PRESENTED HERE. SEE ACTUAL ENTRY IN RTECS FOR COMPLETE INFORMATION.

---------- HEALTH HAZARD DATA ----------

ACUTE EFFECTS

HARMFUL IF SWALLOWED, INHALED, OR ABSORBED THROUGH SKIN.

MAY CAUSE EYE IRRITATION.

MAY CAUSE SKIN IRRITATION.

TO THE BEST OF OUR KNOWLEDGE, THE CHEMICAL, PHYSICAL, AND TOXICOLOGICAL PROPERTIES HAVE NOT BEEN THOROUGHLY INVESTIGATED.

FIRST AID

IN CASE OF CONTACT, IMMEDIATELY FLUSH EYES OR SKIN WITH COPIOUS

AMOUNTS OF WATER FOR AT LEAST 15 MINUTES WHILE REMOVING CONTAMINATED

CLOTHING AND SHOES.

IF INHALED, REMOVE TO FRESH AIR. IF NOT BREATHING GIVE ARTIFICIAL RESPIRATION. IF BREATHING IS DIFFICULT, GIVE OXYGEN.

IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS CONSCIOUS.

CALL A PHYSICIAN.

WASH CONTAMINATED CLOTHING BEFORE REUSE.

---------- PHYSICAL DATA ----------

APPEARANCE AND ODOR

DARK-BROWN OR BLACK FLAKES

---------- FIRE AND EXPLOSION HAZARD DATA ----------

EXTINGUISHING MEDIA

WATER SPRAY.

CARBON DIOXIDE, DRY CHEMICAL POWDER OR APPROPRIATE FOAM.

SPECIAL FIREFIGHTING PROCEDURES

WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING TO
PREVENT CONTACT WITH SKIN AND EYES.
UNUSUAL FIRE AND EXPLOSIONS HAZARDS
EMITS TOXIC FUMES UNDER FIRE CONDITIONS.
---------- REACTIVITY DATA ----------
INCOMPATIBILITIES
STRONG OXIDIZING AGENTS
PROTECT FROM LIGHT.
ACIDS
HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS
TOXIC FUMES OF:
CARBON MONOXIDE, CARBON DIOXIDE
---------- SPILL OR LEAK PROCEDURES ----------
STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED
EVACUATE AREA.
WEAR SELF-CONTAINED BREATHING APPARATUS, RUBBER BOOTS AND HEAVY

RUBBER GLOVES.
SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL.
AVOID RAISING DUST.
VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS COMPLETE.
WASTE DISPOSAL METHOD
DISSOLVE OR MIX THE MATERIAL WITH A COMBUSTIBLE SOLVENT AND BURN IN A
CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER.

OBSERVE ALL FEDERAL, STATE, AND LOCAL LAWS.
--- PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE ---
WEAR APPROPRIATE NIOSH/MSHA-APPROVED RESPIRATOR, CHEMICAL-RESISTANT
GLOVES, SAFETY GOGGLES, OTHER PROTECTIVE CLOTHING.
SAFETY SHOWER AND EYE BATH.
USE ONLY IN A CHEMICAL FUME HOOD.
DO NOT BREATHE DUST.
AVOID CONTACT WITH EYES, SKIN AND CLOTHING.
AVOID PROLONGED OR REPEATED EXPOSURE.
WASH THOROUGHLY AFTER HANDLING.
TOXIC.
KEEP TIGHTLY CLOSED.
LIGHT SENSITIVE
STORE IN A COOL DRY PLACE.
TOXIC BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.
IF YOU FEEL UNWELL, SEEK MEDICAL ADVICE (SHOW THE LABEL WHERE

POSSIBLE).
WEAR SUITABLE PROTECTIVE CLOTHING, GLOVES AND EYE/FACE PROTECTION.

REGULATORY INFORMATION
20.0% SILVER COMPOUND
THIS PRODUCT IS SUBJECT TO SARA SECTION 313 REPORTING REQUIREMENTS.

THE ABOVE INFORMATION IS BELIEVED TO BE CORRECT BUT DOES NOT PURPORT TO BE
ALL INCLUSIVE AND SHALL BE USED ONLY AS A GUIDE. SIGMA ALDRICH SHALL NOT BE
HELD LIABLE FOR ANY DAMAGE RESULTING FROM HANDLING OR FROM CONTACT WITH THE
ABOVE PRODUCT. SEE REVERSE SIDE OF INVOICE OR PACKING SLIP FOR ADDITIONAL
TERMS AND CONDITIONS OF SALE

Sesame Oil (7368-w)

Aceite de Ajonjoli; Benne Oil; Gingelly Oil; Oleum Sesami; Teel Oil.

Pharmacopoeias. In *Aust., Belg., Br., Chin., Eur., Fr., Ger., It., Jpn, Neth., Port.,* and *Swiss.* Also in *USNF.*

Standards of *Ph. Eur.* apply to those countries that are parties to the Convention on the Elaboration of a European Pharmacopoeia, see p.xiii.

The fixed oil obtained from the ripe seeds of *Sesamum indicum* (Pedaliaceae) by expression or extraction and subsequent refining. It is a clear pale yellow oil, almost odourless and with a bland taste with a fatty-acid content consisting mainly of linoleic and oleic acids. It solidifies to a buttery mass at about −4°.

Slightly **soluble** to practically insoluble in alcohol; miscible with carbon disulphide, chloroform, ether, and petroleum spirit. **Store** at a temperature not exceeding 40° in well-filled airtight containers. Protect from light.

Sesame oil has been used in the preparation of liniments, plasters, ointments, and soaps. Because it is relatively stable, it is a useful solvent and vehicle for parenteral products. Hypersensitivity reactions have been observed.

Shellac (285-x)

904; Gomme Laque; Lacca; Lacca in Tabulis; Schellack.

Pharmacopoeias. In *Fr.* and *Ger.* Also in *USNF.*

Jpn includes Purified Shellac and White Shellac (Bleached).

Shellac is obtained by purification of the resinous secretion of the insect *Laccifer lacca* Kerr (Coccidae). The USNF describes 4 grades: Orange Shellac is produced by filtration in the molten state or by a hot solvent process, or both; removal of the wax produces Dewaxed Orange Shellac; Regular Bleached (White) Shellac is prepared by dissolving the secretion in aqueous sodium carbonate, bleaching with hypochlorite, and precipitating with sulphuric acid; removal of the wax by filtration during the process produces Refined Bleached Shellac.

Practically **insoluble** in water; very slowly soluble in alcohol 85% to 95% (w/w); soluble in ether, 13% to 15%, and in aqueous solutions of ethanolamines, alkalis, and borax. **Store** preferably at a temperature not exceeding 8°.

Shellac is used as an enteric coating for pills and tablets, but disintegration time has been reported to increase markedly on storage.

Preparations

Names of preparations are listed below; details are given in Part 3.

Official Preparations

USNF 18: Pharmaceutical Glaze.

Siam Benzoin (273-c)

Benjoin du Laos; Benzoe Tonkinensis.

Pharmacopoeias. In *Aust., Chin., Fr., It.,* and *Swiss.* Also in many pharmacopoeias under the title benzoin and should not be confused with Sumatra Benzoin. *Hung., Jpn,* and *US* allow both Siam benzoin and Sumatra benzoin under the title Benzoin.

A balsamic resin from *Styrax tonkinensis* (Styracaceae) and containing not more than 10% of alcohol (90%)-insoluble matter.

Yellowish-brown to rusty brown compressed pebble-like tears with an agreeable, balsamic, vanilla-like odour. The tears are separated or very slightly agglutinated, milky white on fracture, [illegible] and brittle at ordinary temperatures, but softened [illegible]

Siam benzoin has been used similarly to Sumatra benzoin [illegible] been used as a preservative and was formerly [illegible] aration of benzoinated lard.

Prepar[illegible]

Names of pr[illegible] listed below; details are given in Part 3.

Official Prepa[illegible]

USP 23: Comp[illegible] Tincture; Podophyllum Resin Topical Solution.

Proprietary Prepa[illegible]

Multi-ingredient pre[illegible]s. *Canad.:* Benzoinspray†; Cold Sore Lotion†; *Ital.:* Ondr[illegible] *pain:* Vahos Balsamicos†.

Silver (5316-v)

E174.

[illegible] = 107.8682.

[illegible] — 7440-22-4.

Pharmacopoeias. In *Swiss.*

A pure white, malleable and duct[illegible]l.

Silver possesses antibacterial prop[illegible]nd is used topically either as the metal or as silver salts[illegible]t absorbed to any great extent and the main problem [illegible]ed with the metal is argyria, a general grey discoloration. Silver is used as a colouring agent for some types of confectionery. It is also used as Argentum Metallicum in homeopathy.

Numerous salts or compounds of silver have been employed for various therapeutic purposes, including silver acetate (p.1751), silver allantoinate and silver zinc allantoinate, silver borate, silver carbonate, silver chloride, silver chromate, silver glycerolate, colloidal silver iodide, silver lactate, silver manganite, silver nitrate (p.1751), silver-nylon polymers, silver protein (p.1751), and silver sulphadiazine (p.273).

A report of reversible neuropathy associated with the absorption of silver from an arthroplasty cement.[1]

1. Vik H, *et al.* Neuropathy caused by silver absorption from arthroplasty cement. *Lancet* 1985; **i:** 872.

Coating catheters with silver has been reported to reduce the incidence of catheter-associated bacteriuria,[1,2] but other studies have reported increased infection.[3]

1. Lundeberg T. Prevention of catheter-associated urinary-tract infections by use of silver-impregnated catheters. *Lancet* 1986; **ii:** 1031.
2. Johnson JR, *et al.* Prevention of catheter-associated urinary tract infections with a silver oxide-coated urinary catheter: clinical and microbiologic correlates. *J Infect Dis* 1990; **162:** 1145–50.
3. Riley DK, *et al.* A large randomized clinical trial of a silver-impregnated urinary catheter: lack of efficacy and staphylococcal superinfection. *Am J Med* 1995; **98:** 349–56.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Austral.: Micropur; *Canad.:* Tabanil; *Ger.:* Dulcargan†; Silargeten†.

Multi-ingredient preparations. *Austral.:* Sima-Varix Bandage†; Simanite†; *Fr.:* Stérilet T au Cuivre Argent†; *Ger.:* Adsorgan†; Grüne Salbe "Schmidt" N; *Ital.:* Actisorb Plus; Agipiù; Katoderm; Katoxyn; Nova-T; Silver-Nova T†; *Spain:* Argentocromo; *UK:* Actisorb Plus.

Silver Acetate (5319-p)

Argenti Acetas.

CH_3COOAg = 166.9.

CAS — 563-63-3.

Pharmacopoeias. In *Aust.* and *Hung.*

Silver acetate has been used similarly to silver nitrate as a disinfectant. It has also been used in antismoking preparations.

References.

1. Jensen EJ, *et al.* Serum concentrations and accumulation of silver in skin during three months' treatment with an anti-smoking chewing gum containing silver acetate. *Hum Toxicol* 1988; **7:** 535–40.
2. Gourlay SG, McNeill JJ. Antismoking products. *Med J Aust* 1990; **153:** 699–707.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

UK: Tabmint.

Silver Nitrate (5321-h)

Argenti Nitras; Nitrato de Plata; Nitrato de Prata.

$AgNO_3$ = 169.9.

CAS — 7761-88-8.

Pharmacopoeias. In *Aust., Belg., Br., Cz., Eur., Fr., Ger., Hung., Int., It., Jpn, Neth., Port., Swiss,* and *US.*

The standards of *Ph. Eur.* apply to those countries that are parties to the Convention on the Elaboration of a European Pharmacopoeia, see p.xiii.

Colourless or white transparent crystals or crystalline odourless powder. On exposure to light in the presence of organic matter, silver nitrate becomes grey or greyish-black.

Soluble 1 in 0.4 of water and 1 in 30 of alcohol; its solubility is increased in boiling water or alcohol; slightly soluble in ether. A solution in water has a pH of about 5.5.

Silver nitrate is **incompatible** with a range of substances. Although it is unlikely that there will be a need to add any of the interacting substances to silver nitrate solutions considering its current uses, pharmacists should be aware of the potential for incompatibility. **Store** in airtight non-metallic containers. Protect from light.

The reported yellow-brown discoloration of samples of silver nitrate bladder irrigation (1 in 10 000) probably arose from the reaction of the silver nitrate with alkali released from the glass bottle which appeared to be soda-glass.[1]

1. *PSGB Lab Report P/80/6* 1980.

Adverse Effects

Symptoms of poisoning stem from the corrosive action of silver nitrate and include pain in the mouth, sialorrhoea, diarrhoea, vomiting, coma, and convulsions.

A short lived minor conjunctivitis is common in infants given silver nitrate eye drops; repeated use or the use of high concentrations produces severe damage and even blindness. Chronic application to the conjunctiva, mucous surfaces, or open wounds leads to argyria, which though difficult to treat is considered to be mainly a cosmetic hazard, see under Silver (above).

Absorption of nitrite following reduction of nitrate may cause methaemoglobinaemia. There is also a risk of electrolyte disturbances.

Treatment of these adverse effects is symptomatic.

Silver nitrate from a stick containing 75% was applied to the eyes of a newborn infant instead of a 1% solution.[1] After 1 hour there was a thick purulent secretion, the eyelids were red and oedematous, and the conjunctiva markedly injected. The corneas had a blue-grey bedewed appearance with areas of corneal opacification. After treatment by lavage and topical application of antibiotics and homatropine 2% there was a marked improvement and after 1 week topical application of corticosteroids was started. Residual damage was limited to slight corneal opacity.

1. Hornblass A. Silver nitrate ocular damage in newborns. *JAMA* 1975; **231:** 245.

Pharmacokinetics

Silver nitrate is not readily absorbed.

Uses and Administration

Silver nitrate possesses disinfectant properties and is used in many countries as a 1% solution for the prophylaxis of gonococcal ophthalmia neonatorum (see Neonatal Conjunctivitis, p.151) when 2 drops are instilled into each conjunctival sac of the neonate. However, as it can cause irritation, other agents are often used.

In stick form it has been used as a caustic to destroy warts and other small skin growths. Compresses soaked in a 0.5% solution of silver nitrate have been applied to severe burns to reduce infection. Solutions have also been used as topical disinfectants and astringents in other conditions.

Silver nitrate (Argentum Nitricum; Argent. Nit.) is used in homoeopathic medicine. It is also used in cosmetics to dye eyebrows and eye lashes in a concentration of not more than 4%.

Cystitis. Comment on silver nitrate irrigation having limited value in the management of haemorrhagic cystitis after radiotherapy.[1]

1. Anonymous. Haemorrhagic cystitis after radiotherapy. *Lancet* 1987; **i:** 304–6.

Preparations

Names of preparations are listed below; details are given in Part 3.

Official Preparations

USP 23: Silver Nitrate Ophthalmic Solution; Toughened Silver Nitrate.

Proprietary Preparations

Austral.: Howe's Solution†; Quit†; *Ger.:* Mova Nitrat; Pluralane; *Spain:* Argenpal.

Multi-ingredient preparations. *Austral.:* Super Banish; *Spain:* Argentofenol; *Switz.:* Grafco; *UK:* AVOCA.

Silver Protein (5322-m)

Albumosesilber; Argentoproteinum; Argentum Proteinicum; Protargolum; Proteinato de Plata; Proteinato de Prata; Strong Protargin; Strong Protein Silver; Strong Silver Protein.

CAS — 9007-35-6 (colloidal silver).

NOTE. Synonyms for mild silver protein include: Argentoproteinum Mite; Argentum Vitellinicum; Mild Protargin; Mild Silver Proteinate; Silver Nucleinate; Silver Vitellin; Vitelinato de Plata and Vitelinato de Prata.

Pharmacopoeias. In *Aust., Belg., Cz., Fr., Hung., It.,* and *Jpn.* Many of these pharmacopoeias include monographs on mild silver protein as well as on colloidal silver.

Silver protein solutions have antibacterial properties, due to the presence of low concentrations of ionised silver, and have been used as eye drops and for application to mucous membranes. The mild form of silver protein is considered to be less irritating, but less active.

Colloidal silver which is also a preparation of silver in combination with protein has also been used topically for its antibacterial activity.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

Fr.: Stillargol; Vitargénol.

Multi-ingredient preparations. *Aust.:* Coldargan; *Fr.:* Pastaba; *Ger.:* Coldargan†; *Ital.:* Arscolloid; Bio-Arscolloid; Corti-Arscolloid; Rikosilver; Rinantipiol; Rinovit Nube.

Slippery Elm (5458-t)

Elm Bark; Slippery Elm Bark; Ulmus; Ulmus Fulva.

Pharmacopoeias. In *US.*

The dried inner bark of *Ulmus fulva* (=*U. rubra*) (Ulmaceae).

Slippery elm contains much mucilage and has been used as a demulcent.

Epidermal necrolysis. Based on the treatment of 10 cases, the following was suggested as treatment for toxic epidermal necrolysis: continuous moist compresses of silver nitrate solution 0.25 to 0.5%, with generous wrapping to prevent excessive cooling; daily electrolyte estimations; and daily debridement; after about the fourth day the compresses could be replaced by dexamethasone/neomycin spray followed by inunction of wool alcohols ointment. A penicillin should be given routinely and steroids if vasculitis was present.— P. J. Koblenzer, *Archs Derm.*, 1967, *95*, 608.

Herpes simplex. Silver nitrate 1% had little effect *in vitro* or *in vivo* against herpes simplex virus type 2.— V. R. Coleman *et al.*, *Antimicrob. Ag. Chemother.*, 1973, *4*, 259. A further study.— F. Shimizu *et al.*, *ibid.*, 1976, *10*, 57.

Hydatid cysts. Intrahepatic cysts of *Echinococcus granulosus* were treated with excellent results in 20 patients by freezing the operation area then administering silver nitrate 0.5% to destroy the scolices.— I. Nazarian and F. Saidi, *Z. Tropenmed. Parasit.*, 1971, *22*, 188, per *Trop. Dis. Bull.*, 1971, *68*, 1356.

Ophthalmia neonatorum. In a study of the incidence of ophthalmia neonatorum in 220 000 births, it was found that in 92 865 cases where preparations other than silver nitrate were used the frequency of gonococcal ophthalmia neonatorum was 0.07% whereas where silver nitrate was used the rate was 0.1%. Silver nitrate did not always suppress the development of the condition and seemed no more effective than other agents. While a drop of 1% silver nitrate solution did no harm, there was little evidence that it did any good.— *Lancet*, 1949, *1*, 313.

Of the 49 states of the USA which had made regulations requiring routine prophylactic treatment of the eyes of newborn infants, 22 had specified silver nitrate applications. No evidence had been found to contra-indicate 1% silver nitrate drops when properly packed, handled, and administered. The increasing incidence of gonorrhoea had rendered continued routine prophylaxis necessary.—P.C. Barsam, *New Engl. J. Med.*, 1966, *274*, 731. Fewer local reactions occurred with penicillin than with silver nitrate eye-drops. Penicillin for neonatal prophylaxis should not be abandoned, since it did not appear to sensitise infants.—G. Nathenson (letter), *ibid.*, *275*, 280. Eye-drops containing less than 2% of silver nitrate were considered to be ineffective. Treatment was effective if applied early and prophylaxis was advised only in infants whose mothers were known or suspected to be infected.— E. B. Shaw (letter), *ibid.*, 281. See also P. Kober, *Medsche Klin.*, 1967, *62*, 424.

To prevent gonorrhoeal ophthalmia neonatorum, a 1% solution of silver nitrate was instilled at birth. The chemical conjunctivitis caused by silver nitrate was of short duration.— P. Thygeson, *J. Am. med. Ass.*, 1967, *201*, 902.

For reports on the chemical conjunctivitis associated with instillation of silver nitrate eye-drops and recommendations for reduction of the incidence, see Adverse Effects (above).

Pneumothorax. Spontaneous pneumothorax was successfully treated in 132 patients by pleurodesis induced with silver nitrate; repeated pleurodesis was necessary in only 2 patients. It was suggested that this therapy should be used for patients with only small or no blebs visible on thoracoscopy, or with only mild pre-existing lung disease.— I. Anderson and H. Nissen, *Dis. Chest*, 1968, *54*, 230, per *J. Am. med. Ass.*, 1968, *206*, 681.

Wounds. Silver nitrate solution 0.5% was more effective against Gram-positive than Gram-negative bacteria in the treatment of nonthermal war wounds. The solution did not hinder wound healing or epithelialisation of split thickness skin grafts.— J. P. Connors *et al.*, *Archs Surg., Chicago*, 1969, *98*, 119, per *J. Am. med. Ass.*, 1969, *207*, 580.

Preparations

Mitigated Silver Nitrate *(B.P.C. 1968)*. Argenti Nitras Mitigatus; Mitigated Caustic; Argenti Nitras Dilutus. Silver nitrate 1 and potassium nitrate 2, fused together and suitably moulded for application as a caustic to warts and condylomas. Protect from light.

A similar preparation is included in several pharmacopoeias.

Silver Nitrate Stain Remover *(Univ. of Iowa)*. Thiourea ($NH_2.CS.NH_2$=76.12) 8 g, citric acid monohydrate 8 g, water to 100 ml. It should be freshly prepared.

Toughened Silver Nitrate *(B.P.)*. Argenti Nitras Induratus; Toughened Caustic; Fused Silver Nitrate; Lunar Caustic; Moulded Silver Nitrate; Stylus Argenti Nitrici. Silver nitrate 95 and potassium nitrate 5, fused together and suitably moulded.

White or greyish-white cylindrical rods or cones, which become grey or greyish-black on exposure to light. Freely soluble in water; sparingly soluble in alcohol. Protect from light.

A similar preparation is included in several pharmacopoeias.

Toughened Silver Nitrate *(U.S.P.)*. Contains not less than 94.5% of $AgNO_3$, the remainder consisting of silver chloride. Store in airtight containers. Protect from light.

Creams

Silver Nitrate Cream. Silver nitrate, 0.5 or 2%, Xalifin-15 20%, water to 100%. The cream was stable with only slight discoloration when stored for 4 weeks in the dark at room temperature; at 0° to 4° there was no discoloration.—Pharm. Soc. Lab. Rep. P/68/15, 1968.

Eye-drops

Oculoguttae Argenti Nitratis pro Neonatis *(Dan. Disp.)*. Silver nitrate 670 mg, potassium nitrate 1.2 g, and Water for Injections, 98.13 g.

A similar preparation is included in *F.N.Belg.*

Silver Nitrate Eye-drops *(B.P.C. 1954)*. Gutt. Argent. Nit. Silver nitrate 0.5% w/v, potassium nitrate 1.33% w/v, in Solution for Eye-drops.

Nord. P. has 1% w/w with potassium nitrate 1% w/w in Water for Injections.

Ointments

Unguentum Argenti Nitratis Compositum. Compound Silver Nitrate Ointment. An ointment with this title is included in several pharmacopoeias. It contains silver nitrate 1% and Peru balsam 5 to 10% usually in a basis of yellow soft paraffin or yellow soft paraffin and wool fat.

Ophthalmic Solutions

Silver Nitrate Ophthalmic Solution *(U.S.P.)*. A solution of silver nitrate 0.95 to 1.05% in an aqueous medium. pH 4.5 to 6. It may contain sodium acetate as a buffer. Store in single-dose containers. Protect from light.

Solutions

Ammoniacal Silver Nitrate Solution *(U.S.N.F. XII, 1965)*. Ammoniacal Silver Nitrate, Howe. A solution of diamminosilver nitrate was prepared from silver nitrate 704 g, water 245 ml, and strong ammonia solution to dissolve all but the last trace of precipitate (about 680 ml).It contains 28.5 to 30.5% w/w of Ag and 9 to 9.7% w/w of NH_3. Store in small glass-stoppered containers or in ampoules. Protect from light.

This solution has been employed in dental surgery to deposit silver in exposed dentine or to fill up small crevices in the teeth. After the solution had been applied to the tooth it was followed by a reducing agent such as a 10% formaldehyde solution or eugenol to cause a deposit of metallic silver. The solution has also been employed in the treatment of fungous infections of the nails.

Solutio Argenti Nitratis cum Tetracaino *(Nord. P.)*. Silver nitrate 200 mg, amethocaine nitrate 100 mg, and water 99.7 g.

Proprietary Names

Helvedstensstifter *(Braun, Denm.)*; Lapis *(DAK, Denm.)*; Mova Nitrat Pippette *(Lindopharm, Ger.)*.

5322-m

Silver Protein *(B.P.C. 1968)*. Argentoproteinum; Strong Protein Silver; Strong Protargin; Argentum Proteinicum; Albumosesilber; Protargolum; Proteinato de Plata; Proteinato de Prata.

CAS — 9015-51-4.

Pharmacopoeias. In *Arg., Aust., Belg., Cz., Fr., Hung., Ind., Int., It., Jap., Pol., Port., Roum., Span.,* and *Turk.*

A brown odourless hygroscopic powder containing 7.5 to 8.5% of Ag.

Slowly **soluble** 1 in 2 of water; very slightly soluble in alcohol, chloroform, and ether. A solution in water is neutral to litmus. Solutions may be prepared by shaking the powder over the surface of cold water and allowing it to dissolve slowly, or by triturating the powder to a cream with water and diluting. Solutions are transparent and not coagulated by heat, nor precipitated by the addition of alkali, alkali sulphides, alkali salts, or albumin; they are relatively non-staining. Store in airtight containers. Protect from light.

Adverse Effects. As for Silver (above).

Uses. Silver protein solutions have antibacterial properties, due to the presence of low concentrations of ionised silver, and are used as eye-drops in the treatment of conjunctivitis. Solutions are relatively non-irritant unless they contain more than 10% of silver protein.

Preparations

Silver Protein Eye-drops *(B.P.C. 1963)*. Gutt. [illegible] rot. A solution of silver protein 5%, with phe[illegible] acetate or nitrate 0.002%, in water. Prepared [illegible] ving, aseptically, the silver protein in a [illegible] solution of phenylmercuric acetate or nitrate [illegible] ferring to the final sterilised container. Th[illegible] must be freshly prepared. They are advers[illegible] by alkali. Protect from light.

Proprietary Names

Stillargol *(Mayoly-Spindler, Fr.)*.

5323-b

Mild Silver Protein *(B.P.C. 1968)*. Argento[illegible] Mite; Argentum Vitellinicum; Mild Silver Pro[illegible] Silver Nucleinate; Silver Vitellin; Mild Prota[illegible] nato de Plata; Vitelinato de Prata.

NOTE. The name Mild Silver Protein is [illegible] compound because it is less bactericidal and [illegible] than Silver Protein, though it contains more [illegible]

Pharmacopoeias. In *Arg., Belg., Fr., Ind.,* [illegible] *Roum., Span., Swiss,* and *Turk.*

A hydroscopic brown powder or nearly black [illegible] granules with a slight odour and taste, contain[illegible] 23% of Ag.

Soluble slowly but completely in water; [illegible] soluble in alcohol, chloroform, and ether. After [illegible] to light it is incompletely soluble in water. [illegible] solution in water is iso-osmotic with serum. In[illegible] with cocaine hydrochloride, but compatible [illegible] atropine sulphate solution. Incompatible with [illegible] acids, alkalis, tannins, and oxidising agents. [illegible] airtight containers. Protect from light.

Preservative for eye-drops. Phenylmercur[illegible] 0.005% was a suitable preservative for [illegible] protein eye-drops sterilised by heating at 98[illegible] for 30 minutes.— M. Van Ooteghem, *Pharm*[illegible] *Belg.*, 1968, *45*, 69.

Adverse Effects, Treatment, and Precautions [illegible] Silver (above).

Argyria. Argyria developed in an elderly [illegible] prolonged use of mild silver protein 10% nasal [illegible] W. A. Parker, *Am. J. Hosp. Pharm.*, 1977, *34*, [illegible]

Uses. Mild silver protein solutions have anti[illegible] properties similar to those of silver protein solu[illegible] they contain even lower concentrations of ioni[illegible] and are consequently less irritant to the ti[illegible] silver protein may be used, therefore, in higher [illegible] trations than silver protein, particularly whe[illegible] important to avoid irritation of mucous [illegible] Mild silver protein, usually 1 to 5%, is used [illegible] rine as drops or as a spray in nasal infectio[illegible] been applied as a 20% solution in conjunctivit[illegible] the prophylaxis of ophthalmia neonatorum and [illegible] solution to corneal ulcers.

Rhinitis. Mild silver protein (Argyrol) has bee[illegible] many years in children with chronic purulen[illegible] and has some value in encouraging nose blo[illegible] main disadvantage is the irreversible staining [illegible] kerchiefs and pillows.— D. F. N. Harrison, *Pr*[illegible] *J.*, 1976, *16*, 69.

Preparations

Mild Silver Protein Eye-drops *(B.P.C. 196*[illegible] Argentoprot. Mit. A solution of mild silver pro[illegible] with phenylmercuric acetate or nitrate 0.002% [illegible] Prepared by dissolving, aseptically, the mil[illegible] protein in a sterile 0.002% solution of pheny[illegible] acetate or nitrate and transferring to the final [illegible] container. The eye-drops must be freshly prepa[illegible] are adversely affected by alkali. Protect from li[illegible] *A.P.F.* (Mild Silver Protein Eye-Drops) has [illegible] protein 20% and phenylmercuric nitrate 0.002[illegible] Water for Injections.

Silver Protein and Ephedrine Instillation *(A.P.F.*[illegible] Protein and Ephedrine Nasal Drops. Mild silver [illegible] 5 g, ephedrine 500 mg, phenylmercuric nitrate [illegible] freshly boiled and cooled water to 100 ml. This [illegible] should be recently prepared. Protect from light.

Proprietary Preparations

Argotone *(Rona, UK)*. Contains mild silver [illegible] and ephedrine hydrochloride 0.9% in 0.5[illegible] chloride solution, available as **Nasal Drop**[illegible] **Ready-Spray** nasal spray in plastic atomisers.

Other Proprietary Names

Argincolor *(Fr.)*; Argirol *(Spain)*; Vitargénol *(Fr.*[illegible]

ighly with hot 3 per cent hydro-
eight of the precipitate so obtained
n.
er Iodide in tight, light-resistant

TRATE SOLUTION

mmoniacal Silver Nitrate, Howe

a solution of silver diammino
equivalent of not less than 28.5
and not less than 9.0 Gm. and

. . . . .	704 Gm.
. . . . .	245 ml.
. . . . .	680 ml.
. . . . .	1000 ml.

ortar and dissolve it in the puri-
l t[illegible]om temperature and add
e [illegible] all but the last trace of
his last trace of precipitate from

ion is a clear, colorless, almost odorless
ected by light. Its specific gravity is

ate Solution (1 in 10) responds to the
ate, page 683.
Solution add a few drops of formalde-
recipitate is immediately formed (*dis-
monium nitrates*).
Silver Nitrate Solution (1 in 10) add
filter, add 5 ml. of sodium hydroxide
itmus blue.
remains free from even a transient blue

niacal Silver Nitrate Solution add 3 ml.
the clear filtrate tested in a flame on a
of sodium or potassium (*distinction from*

ml. of Ammoniacal Silver Nitrate Solu-
water, 10 ml. of diluted nitric acid, and
rate with 0.1 *N* ammonium thiocyanate.
is equivalent to 10.79 mg. of Ag.
ut 1 ml. of Ammoniacal Silver Nitrate
e sample to a Kjeldahl distillation flask

with 50 ml. of water, and add sufficient of the water to make a volume of 200 ml.; add 10 ml. of sodium sulfide T.S. and 20 ml. of a solution of sodium hydroxide (4 in 10). Connect the flask to a condenser, the lower outlet tube of which dips beneath the surface of 50 ml. of 0.5 *N* sulfuric acid contained in a receiving flask. Distil the mixture until about 100 ml. of distillate has been collected, add methyl red T.S., and titrate the excess acid with 0.5 *N* sodium hydroxide. Each ml. of 0.5 *N* sulfuric acid is equivalent to 8.516 mg. of NH_3.

The ratio between the percentage of ammonia and the percentage of silver closely approximates 1 to 3.16.

Packaging and storage—Preserve Ammoniacal Silver Nitrate Solution in small glass-stoppered, light-resistant containers, or in light-resistant ampuls.

FOR TOPICAL USE—Mix Ammoniacal Silver Nitrate Solution with a reducing agent, such as formaldehyde (1 in 10) or eugenol, to deposit the metallic silver, in a state of fine subdivision, in the desired area of the tooth.

CATEGORY—Protective (dental).

Silver Protein, Mild

MILD SILVER PROTEIN

Argentum Proteinicum Mite — Mild Protargin

Mild Silver Protein is silver rendered colloidal by the presence of, or combination with, protein. It contains not less than 19 per cent and not more than 23 per cent of Ag.

Caution: Solutions of Mild Silver Protein should be freshly prepared or contain a suitable stabilizer, and should be dispensed in amber-colored bottles!

Description—Mild Silver Protein occurs as dark brown or almost black, shining scales or granules. It is odorless, is frequently hygroscopic, and is affected by light.

Solubility—Mild Silver Protein is freely soluble in water, but almost insoluble in alcohol, in chloroform, and in ether.

Identification—

A: Heat about 100 mg. of Mild Silver Protein in a porcelain crucible until all carbonaceous matter is burned off, warm the residue with 1 ml. of nitric acid, dilute with 10 ml. of water, and add a few drops of hydrochloric acid: a white precipitate is produced which dissolves in ammonia T.S.

B: Ferric chloride T.S. added to a solution of Mild Silver Protein (1 in 100) discharges the dark color and a precipitate is gradually produced.

C: To 10 ml. of a solution of Mild Silver Protein (1 in 100) add a few drops of mercury bichloride T.S.: a white precipitate is formed and the supernatant liquid becomes colorless or nearly so.

Ionic silver—To 10 ml. of a solution of Mild Silver Protein (1 in 100) add 2 ml. of a solution of sodium chloride (1 in 100): no turbidity is produced.

Distinction from strong silver protein—Dissolve 1 Gm. of Mild Silver Protein in 10 ml. of water. Add, all at once, 7 Gm. of ammonium sulfate, and stir occasionally for 30 minutes. Filter through quantitative filter paper into a 50-ml. Nessler tube, returning the first portions of the filtrate to the filter, if necessary, to secure a clear filtrate, and allow the filter and precipitate to drain. Add to the clear filtrate 25 ml. of a solution of acacia (1 in 100). In a second 50-ml. Nessler tube dissolve 7 Gm. of ammonium sulfate in 10 ml. of water, and add to this solution 25 ml. of the solution of acacia and 1.6 ml. of 0.01 *N* silver nitrate. To each tube

Database: Medline <1966 to present>

<1>
Unique Identifier
83203583
Authors
Isenberg S. Apt L. Yoshimuri R.
Title
Chemical preparation of the eye in ophthalmic surgery. II. Effectiveness of mild silver protein solution.
Source
Archives of Ophthalmology. 101(5):764-5, 1983 May.
Abstract
Although a mild silver protein solution (Argyrol) has been used for a number of years and is still used by many ophthalmic surgeons, its efficiency as an antibacterial agent on the conjunctiva has not been scientifically evaluated as part of the preoperative chemical preparation of the eye. We studied the effectiveness of a mild silver protein solution on the conjunctival flora of 32 patients in a masked fashion. By bacteriologic analysis, the mild silver protein solution was found to be no more effective in reducing the number of species and colonies in the treated eye than in the untreated eye. While the mild silver protein solution does stain mucus and other debris on the eye to facilitate irrigation, this study did not demonstrate a significant bactericidal effect.

<2>
Unique Identifier
83142687
Authors
Apt L. Isenberg S.
Title
Chemical preparation of skin and eye in ophthalmic surgery: an international survey.
Source
Ophthalmic Surgery. 13(12):1026-9, 1982 Dec.
Abstract
We surveyed 214 ophthalmologists worldwide to learn their methods of preoperative chemical preparation of eye and skin. A 96.8% return rate was achieved. While a wide diversity of agents was reported, povidone-iodine was the most popular agent applied to the skin. The conjunctiva usually was either ignored or rinsed with a saline solution by the respondents. Almost a quarter used mild silver

protein (Argyrol) on the conjunctiva. Most of the preparation is performed by the physician rather than the nurse. Review of the advantages and pitfalls of the agents reported should cause the ophthalmologist to reconsider these agents for their effectiveness, spectrum, and duration of action.

Chemical Preparation of the Eye in Ophthalmic Surgery

II. Effectiveness of Mild Silver Protein Solution

Sherwin Isenberg, MD; Leonard Apt, MD; Robert Yoshimuri, PhD

• **Although a mild silver protein solution (Argyrol) has been used for a number of years and is still used by many ophthalmic surgeons, its efficiency as an antibacterial agent on the conjunctiva has not been scientifically evaluated as part of the preoperative chemical preparation of the eye. We studied the effectiveness of a mild silver protein solution on the conjunctival flora of 32 patients in a masked fashion. By bacteriologic analysis, the mild silver protein solution was found to be no more effective in reducing the number of species and colonies in the treated eye than in the untreated eye. While the mild silver protein solution does stain mucus and other debris on the eye to facilitate irrigation, this study did not demonstrate a significant bactericidal effect.**

(*Arch Ophthalmol* 1983;101:764-765)

Therapeutic properties of silver and its salts were recognized as early as the Roman Empire period. Jabir ibn Hayyan Geber, an Arabian physician of the eighth century, initiated the use of silver nitrate on the eye.[1] Carl Siegmund Franz Credé began the prophylactic application of silver nitrate on the eyes of newborn infants to prevent gonococcal conjunctivitis in 1884. After that, silver nitrate was used for other ophthalmic disorders, but it was found occasionally to cause necrosis of conjunctival epithelial cells and a gray-black color when light reduced the salt to its metallic state. In addition, irritation, scarring of the conjunctiva, corneal opacification, and symblepharon occurred. In an attempt to reduce these problems, Albert C. Barnes, MD, and Hermann Hille, in 1902, developed a combination of silver nitrate and grain protein (Argyrol).[2] However, this drug also caused complications. In 1980, Spencer et al[3] reported the clinical and histopathologic findings in one patient who drank this mild silver protein solution for years and in a second patient who applied mild silver protein drops to one eye for a long-term period.

A 20% mild silver protein solution is available for topical ocular use in the United States as a silver nitrate and gelatin colloid. The drug is available also abroad under a variety of proprietary names and formulations. It is classified in pharmacy textbooks as a local anti-infective agent.

The antimicrobial properties of this mild silver protein solution have been questioned for years.[4-7] To our knowledge, there has been no controlled clinical study proving the antibiotic efficacy of this mild silver protein solution as part of the chemical preparation of the eye before surgery. Yet, in a recent international survey of ophthalmologists, Apt and Isenberg[8] found that 22% of the respondents use this mild silver protein solution on the conjunctiva as part of the preoperative chemical preparation of the eye. We, therefore, conducted a masked study to investigate the effectiveness of this mild silver protein solution as an antimicrobial agent in the preoperative preparation.

Accepted for publication Oct 22, 1982.

From the Departments of Ophthalmology (Drs Isenberg and Apt) and Pathology (Dr Yoshimuri), Jules Stein Eye Institute and Harbor-UCLA Medical Center, UCLA School of Medicine.

Reprint requests to the Jules Stein Eye Institute, UCLA School of Medicine, Los Angeles, CA 90024 (Dr Isenberg).

PATIENTS AND METHODS

Thirty-two patients undergoing ophthalmic surgery were studied. No patient had received preoperative antibiotic therapy or had an active infection at the time of surgery.

All subjects had the identical regimen of preoperative preparation. Initially, a sterile anaerobic transport swab was applied to either the inferonasal or inferotemporal conjunctival fornix of one eye and a second swab was applied to the conjunctiva of the same quadrant in the second eye. Twenty microliters (1 drop) of 20% mild silver protein solution then was instilled in the inferior conjunctival fornix of one randomly selected eye. This eye may have been the eye that was operated on when unilateral ocular surgery was performed. Hexachlorophene soap was applied equally to both eyelids, eyelid margins, cheeks, nose, eyebrow, and forehead. The inferior fornix of the eye into which the mild silver protein solution had been instilled was then irrigated with a normal saline solution, while the other eye had no irrigation. Gauze sponges moistened in a saline solution were used to rinse areas bearing hexachlorophene. Next, the quadrant of each inferior conjunctival fornix not previously cultured was cultured with a third and fourth sterile anaerobic transport swab. The choice of which portion of the fornix was cultured before and after the preparation was randomly assigned. Nursing personnel coded each specimen before bacteriologic analysis. The microbiologist had no knowledge of the exact origin of the specimen.

The swab was washed three times in 0.5 mL of Schaedler's broth and wrung out by pressing it along the sides of the tube. The swab was cultured in 10 mL of Schaedler's broth. Blood and chocolate agar each were inoculated with 0.1 mL of eluant and spread on the surface of the agar with a

Table 1.—Mean Number of Colonies and Species of Bacteria Isolated per Subject

	Eye	Mean ± SD: Before Preparation	Mean ± SD: After Preparation	% of Increase
Colonies	Untreated	183 ± 425	284 ± 571	55
	Mild silver protein-treated	231 ± 687	323 ± 750	40
Species	Untreated	1.06 ± 0.83	1.41 ± 0.86	33
	Mild silver protein-treated	1.06 ± 0.75	1.31 ± 0.77	24

Table 2.—Number of Eyes in Which Culture Was Sterile

Type of Eye	No. of Eyes That Were Sterile: Before Preparation	After Preparation	No. of Eyes That Remained Sterile
Untreated	8	4	2
Mild silver protein-treated	7	5	1

glass rod. The blood agar plates were incubated for seven days at 35 °C in an anaerobic jar with a gas mixture of 80% nitrogen, 10% carbon dioxide, and 10% hydrogen. The chocolate agar plates were incubated in 5% to 10% carbon dioxide at 35 °C. After incubation, the colonies were differentiated and enumerated by standard bacteriologic procedures.

RESULTS

Table 1 gives the mean number of colonies and species per subject isolated from untreated and experimental eyes before and after instillation of this mild silver protein solution. Although the number of colonies and species were greater after the preparation than before in both mild silver protein solution-treated and untreated eyes, in no case was the increase of actual numbers significant at the 5% level by Student's *t* test. The difference in the amount of increase of actual number in the untreated eye as opposed to the mild silver protein solution-treated eye also was not found to be significant at the 5% level.

The pattern of sterile cultures before and after chemical preparation of the eye is given in Table 2. Of all the eyes in this study, only three of the 15 that were sterile before preparation remained sterile after preparation.

The organisms cultured were diphtheroids, *Staphylococcus epidermidis*, *Propionibacterium acnes*, *Candida albicans*, and *Klebsiella* sp.

COMMENT

This mild silver protein solution originally was intended to be an antimicrobial agent. The colloidal suspension liberates silver ions that alter the protein in the bacterial cell wall. It also has been suggested that silver interferes with essential metabolic activity of bacteria.[4] The silver in this mild silver protein solution ionizes poorly, and thus causes less irritation than silver nitrate. However, its germicidal effectiveness is also decreased. Pharmacologists have written that "colloidal silver preparations are now in a deserved oblivion."[4] Duke-Elder expressed the opinion that this mild silver protein solution has "little bactericidal action since few free ions are liberated."[1] Havener noted that "Argyrol is one of the poorest germicides."[5] None of these authors cited a controlled study on humans to support their assertions. Despite these negative opinions, almost a quarter of the 214 ophthalmologists surveyed in a large international study (with a 96%-response rate) continue to use this mild silver protein solution in the preoperative chemical preparation of the eye.[8] This investigation, using detailed bacteriologic analysis, was unable to verify that the application of this mild silver protein solution on the eye in vivo was significantly better than an untreated eye in reducing the number of microorganisms on the conjunctiva.

Another property of this mild silver protein solution contributes to its popularity. This mild silver protein solution has the capability of darkly staining mucus or debris present on the conjunctiva, eyelids, or skin. It therefore serves as a marker for the adequacy of the preoperative surgical preparation of the eye. The surgeon may then irrigate any remaining mucus and debris from the eye. Indeed, in the international survey by Apt and Isenberg,[8] many respondents commented that they used it mainly to distinguish mucus and debris in the preparation. However, this positive aspect of the tested mild silver protein solution must be weighed against our recent finding that irrigation itself increases the bacterial flora of the conjunctiva (see p 761).

In the design of this study, it was decided to irrigate the conjunctiva of the eye receiving the mild silver protein solution as is commonly practiced. The control eye received no irrigation in light of our aforementioned findings. Thus, any increased degree of antisepsis obtained by the mild silver protein solution may be offset by the increase in bacterial flora engendered by irrigation.

A frequently cited study of the effectiveness of the tested mild silver protein solution and other agents is that of Thompson et al[6] published in 1937. Of the ten bactericidal agents they studied, our tested mild silver protein solution (Argyrol) had the second highest percentage of surviving organisms after one and ten minutes of exposure. Although the investigation by Thompson et al was performed on the conjunctiva of rabbits, doubts about the effectiveness of our tested mild silver protein solution should have been raised at that time. On the human conjunctiva, our study did not find a significant bactericidal effect of this mild silver protein solution when investigated in a masked fashion.

References

1. Antiseptics, in *The Foundations of Ophthalmology: Heredity, Pathology, Diagnosis, and Therapeutics*, vol 7, in Duke-Elder S (ed): *System of Ophthalmology*. St Louis, CV Mosby Co, 1962, p 635.
2. Schaet W: Argyrol and a byproduct, in *Art and Argyrol*. New York, Yoseloff Co, 1960, pp 47-53.
3. Spencer WH, Garron LK, Contreras F, et al: Endogenous and exogenous ocular and systemic silver deposition. *Trans Ophthalmol Soc UK* 1980;100:171-178.
4. Harvey SC: Antiseptics and disinfectants, fungicides, ectoparasiticides, in Gilman AG, Goodman LS, Gilman A (eds): *The Pharmacological Basis of Therapeutics*, ed 6. New York, Macmillan Publishing Co Inc, 1980, pp 976-977.
5. Havener WH: Germicides, in *Ocular Pharmacology*, ed 4. St Louis, CV Mosby Co, 1978, p 425.
6. Thompson R, Isaacs ML, Khorazo D: A laboratory study of some antiseptics with reference to ocular application. *Am J Ophthalmol* 1937;20:1087-1098.
7. King JH, Wadsworth JAC: *An Atlas of Ophthalmic Surgery*, ed 3. Philadelphia, Harper & Row Publishers Inc, 1981, p 3.
8. Apt L, Isenberg S: Chemical preparation of skin and eye in ophthalmic surgery: An international survey. *Ophthalmic Surg* 1982;13:1026-1029.

Chemical Preparation of Skin and Eye in Ophthalmic Surgery: An International Survey

Leonard Apt, M.D.
Sherwin Isenberg, M.D.

SUMMARY

We surveyed 214 ophthalmologists worldwide to learn their methods of preoperative chemical preparation of eye and skin. A 96.8% return rate was achieved. While a wide diversity of agents was reported, povidone-iodine was the most popular agent applied to the skin. The conjunctiva usually was either ignored or rinsed with a saline solution by the respondents. Almost a quarter used mild silver protein (Argyrol) on the conjunctiva. Most of the preparation is performed by the physician rather than the nurse. Review of the advantages and pitfalls of the agents reported should cause the ophthalmologist to reconsider these agents for their effectiveness, spectrum, and duration of action.

Since the studies of Carl Eberth in 1875, surgeons have known that bacteria are found in hair follicles, sweat glands, and in both the superficial and deeper layers of the skin.[1] Joseph Lister's carbolic acid in spray form, or soaked in gauze and laid on the skin, was the first attempt at preoperative antisepsis. Subsequently, other techniques for achieving preoperative asepsis of the operative field have evolved.

Today, in the course of training in ophthalmic surgery, or when visiting different institutions, one often sees different techniques in preoperative chemical preparation of the eye. The main reasons given for using a certain regimen are tradition and the impression of effectiveness. A scientific rationale rarely is mentioned. To learn the preferences of many ophthalmologists throughout the world, and to determine whether a consensus on a specific regimen exists, we undertook a survey. This information is not found in the ophthalmic literature. The survey was not intended to answer questions definitively about the best method and choice of agents.

MATERIALS AND METHODS

Questionnaires were mailed to 221 ophthalmologists of which 214 were answered and returned. This return rate is 96.8%. In order to obtain a representative sample, abou half of the questionnaires were sent to well-know ophthalmic surgeons at academic institutions and half t prominent private practitioners of ophthalmology. Te percent of the questionnaires were answered by wide known ophthalmic surgeons from such foreign countries a Mexico, Belgium, Japan, Argentina, Canada, German Great Britain, and Switzerland.

The first series of questions asked concerned th sequence of solutions applied to the skin, the duration application, and the area of the face receiving th application. The second series of questions dealt wi solutions intentionally placed on the conjunctiva, duratic of application, and what was used as the rinsing agent. Th third question asked what proportion of the preparatic was done by a physician, nurse, or other nonphysicia Finally, additional comments were requested.

RESULTS

There was considerable disparity in the types ar sequence of agents placed on the skin (Table 1). Howeve 67.5% of the respondents used povidone-iodine produc (as Betadine, Isodine, Prepodyne, Septodyne) somewhe in the preparation, while hexachlorophene (pHisoHex) w used by 16.5%, and aqueous iodine solution was used 12.6% somewhere in the preparation. The most freque regimen of all, used by a third of the respondents, w povidone-iodine solution on the skin followed by a rinse alcohol. The term "rinse" includes saline, sterile wate lactated Ringer solution, balanced salt solution, or simil product (Figure 1). Half of the respondents used a sing

From the Department of Ophthalmology, Jules Stein Eye Institute, UCLA School of Medicine, Los Angeles, California.

Requests for reprints should be addressed to Leonard Apt, M.D., Jules Stein Eye Institute, UCLA School of Medicine, Los Angeles, California 90024.

TABLE 1

ROUTINE OF CHEMICAL AGENTS USED FOR SKIN PREPARATION (n=196)

Multiple Agents	Percent
Povidone-iodine soap → rinse* → Povidone-iodine solution ± alcohol	15.0
Soap → rinse → Povidone-iodine solution ± rinse or alcohol	7.3
Hexachlorophene ± alcohol or rinse → Povidone-iodine ± alcohol or rinse	7.3
Soap ± rinse ± alcohol ± rinse	4.0
Soap ± rinse ± Iodine ± alcohol	3.9
Hexachlorophene → rinse → Iodine ± alcohol	2.4
Hexachlorophene → rinse → merthiolate	1.5
Povidone-iodine → rinse → Iodine	1.0
Alcohol → Povidone-iodine	1.0
Single Agents → Rinse or Alcohol	
Povidone-iodine	32.5
Iodine 1%	4.8
Hexachlorophene	4.3
Zephiran	2.9
Chlorhexidene 1%	2.4
Cerfen	1.0
Merthiolate	1.0
Alcohol	1.0
Don't know	1.0

**Rinse = saline solution, sterile water, lactated Ringer solution, balanced salt solution, or similar product*

TABLE 2

CHEMICAL AGENTS INTENTIONALLY PLACED ON THE CONJUNCTIVA (n=206)

Chemical Agent	Percent
Normal Saline	34.5
Nothing	26.7
Argyrol ± rinse	22.3
Balanced salt solution	5.3
Betadine solution (diluted)	2.4
Neosporin ± rinse	2.0
Ringer solution	1.5
Chlorhexidine	1.0
Sterile water	1.0
Chloramphenicol	1.0
Mercury bichloride	1.0
Gentamycin	0.5
Gentamycin mix	0.5
know	0.5

8 deferred or did not answer

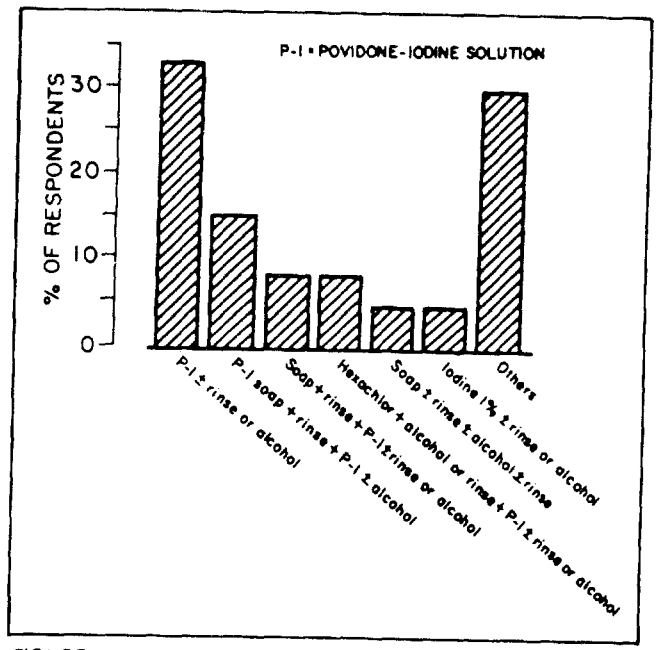


FIGURE 1. (Apt and Isenberg) Percentage of respondents using a particular chemical agent on the skin as part of the preoperative preparation.

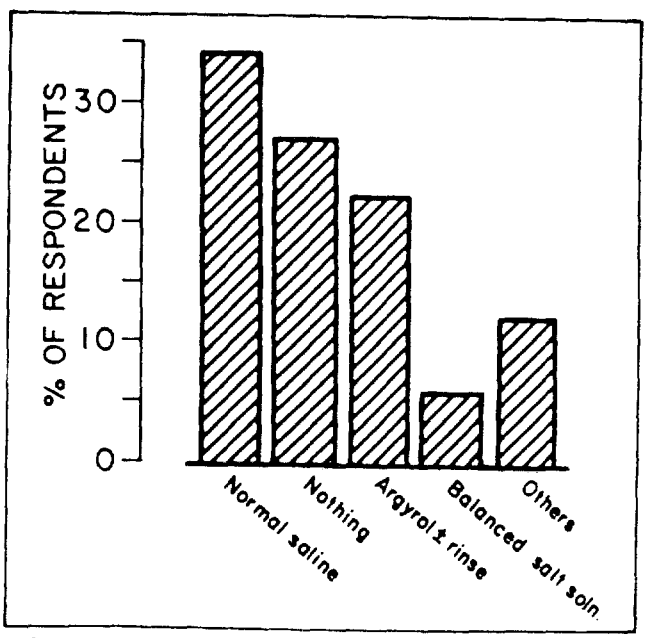


FIGURE 2. (Apt and Isenberg) Percentage of respondents using a particular chemical agent on the conjunctiva as part of the preoperative preparation.

primary agent (such as aqueous iodine, hexachlorophene, or a povidone-iodine product) followed by a rinse or alcohol, while half used a combination of primary agents (Table 1).

The amount of time that these agents were applied to the skin varied from one second to several minutes. So much variation in the length of time was reported as to make

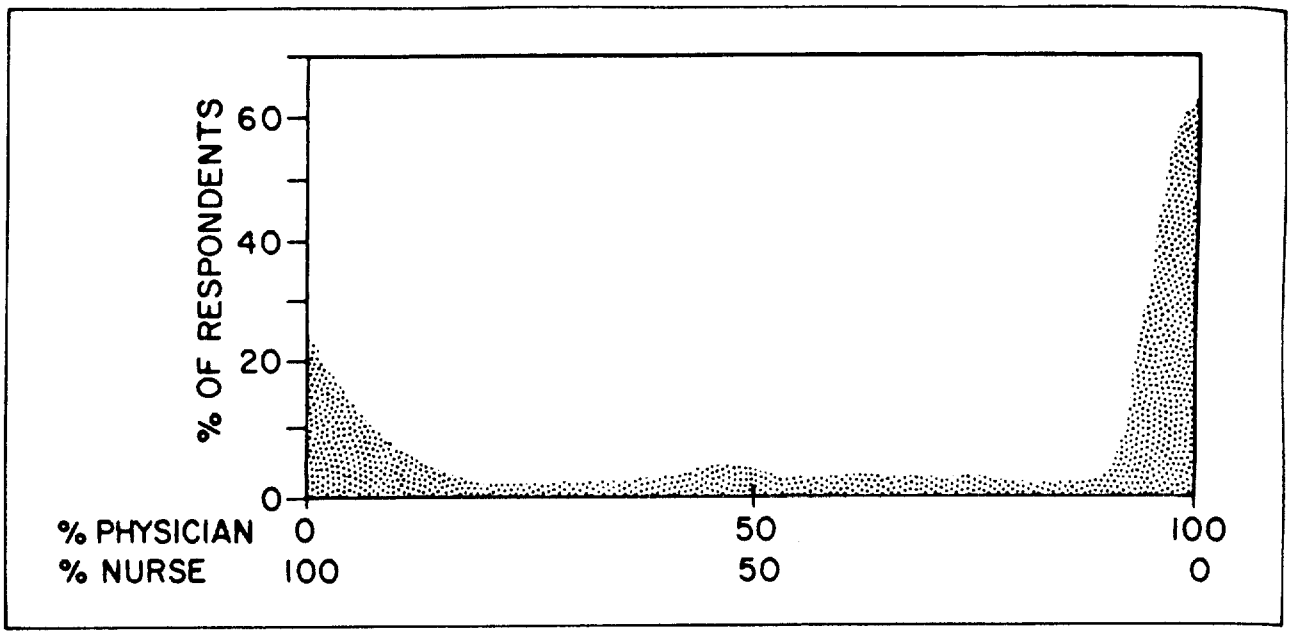


FIGURE 3. (Apt and Isenberg). Relative proportion of physicians compared with nurses performing preoperative preparation of the eye.

TABLE 3

HOW MUCH IS DONE BY PHYSICIAN RELATIVE TO NURSE (n=205)

Physician/Nurse	Percent
100%/ 0	62.0
98%/ 2%	0.5
90%/ 10%	0.5
80%/ 20%	1.0
75%/ 25%	1.0
50%/ 50%	2.9
25%/ 75%	1.5
20%/ 80%	0.5
15%/ 85%	0.5
10%/ 90%	4.4
0 100%	29.4
Not known	0.5

9 deferred or did not answer

conclusions difficult. The facial areas treated were almost universally the forehead, both eyelids, the cheeks, and the nose.

Some ophthalmic surgeons intentionally place solutions on the conjunctiva while others do not (Table 2). About a quarter of the respondents place nothing on the conjunctiva. Forty-two percent simply rinse the conjunctiva with saline solution, balanced salt solution, Ringer solution, or sterile water. Only 31% use a solution bearing any antimicrobial properties. Of the latter, mild silver protein (Argyrol) is by far the most frequently used (Figure 2).

In general, more physicians than nurses perform the preoperative preparation. Sixty-two percent of the respondents indicated that the physician does the entire preparation, while 29% reported that the nurse does the entire preparation. The rest of the respondents answered that the physician and nurse each do part of the preparation (Table 3 and Figure 3).

COMMENT

The validity of this survey was enhanced by the broad spectrum of ophthalmologists contacted, including subspecialists and general ophthalmologists, academicians and nonacademicians, Americans and foreigners, and younger and senior ophthalmologists. The highly satisfactory rate of returned questionnaires (96.8%) also attests to the validity of this survey.

While all ophthalmologists use a form of chemical preparation for the eye prior to surgery, there has been little recent mention or study of this subject in the ophthalmic literature. A lack of interest in this subject was exhibited by some ophthalmologists who replied that they did not know what agents were used in preparation of the operative field. To answer this survey, these surgeons had to obtain the information from others, usually the surgical nurse. The great disparity found in this study in the chemical agents chosen also indicates a lack of recent scientific interest in this topic. In 1951, Maumenee and Michler compared five different techniques for sterilizing the operative field that were then popular.[3] These five techniques were soap and saline, either alone or followed by merthiolate or aqueous iodine, and hexachlorophene and saline followed by either benzalkonium chloride or aqueous iodine and alcohol. In our survey, about 11% of the respondents still used one of these techniques. The advent of povidone-iodine, first experimentally in the 1960s and then clinically in the early

70s, changed the techniques of many ophthalmologists.[1-4] In fact, this survey showed that povidone-iodine is currently the single most popular agent for use in chemical preparation of the skin prior to ophthalmic surgery in this country.

Povidone (polyvinylpyrrolidone) is a polymer with surfactant properties that combines easily with iodine. About two thirds of the iodine remains in the elemental state and is slowly released for antibiotic activity. Aqueous solutions of iodine can cause toxicity to the skin and corneal epithelium, and inflammatory changes in the conjunctiva. But if iodine is combined with povidone these problems are less common and of lesser magnitude. Povidone-iodine has been shown to be bactericidal and virucidal in dilute solutions within minutes in vitro.[5] Given the proper concentration and enough contact time, it is effective even against fungi and spores.

There is more consensus among ophthalmologists in regard to the immediate preoperative preparation of the conjunctiva. More than two thirds of the respondents either ignore the conjunctiva or merely irrigate it. Irrigation presumably would remove mucus or other debris, but would not bear any significant antimicrobial action. Only 31% of the reports indicated the use of an antimicrobial agent on the conjunctiva just prior to surgery. However, some ophthalmologists may have used topical antibiotics on the conjunctiva in the days preceding surgery. Whether latter practice truly sterilizes the conjunctiva, or permits ctive growth of resistant bacteria or regrowth of the iginal bacteria if a bacteriostatic drug is used, is controversial.[6] Argyrol was the agent most commonly used on the conjunctiva by those who used antimicrobial agents at the time of surgery. Some individuals commented that Argyrol was used because it stains the mucus and other debris, which then can be specifically removed by irrigation, and not necessarily because of its antimicrobial properties.

In reviewing the different combinations of chemicals used to sterilize the skin, some comments of practical importance are indicated. If a soap or scrub is used, either as povidone-iodine, another antimicrobial agent, or simple soap, one should be careful to avoid inadvertent entry of these chemicals onto the conjunctiva. Vascular dilation, hyperemia, and possible corneal damage could result from soap or detergent instillation. Potentially this could lead to more hemorrhage if the conjunctiva is incised. One could place a vasoconstrictor on the conjunctiva before and after the preparation to minimize this problem. Some vasoconstrictors such as phenylephrine will dilate the pupil, while others such as naphazoline will not.

Hexachlorophene is bacteriostatic and is more effective against gram-positive than gram-negative bacteria. It is important to know that a single application of hexachlorophene, as used by some surgeons, has little antimicrobial activity. To be maximally effective, hexachlorophene should be applied at least daily beginning five to seven days prior to surgery. The film of hexachlorophene then produced enhances its antimicrobial effects. Alcohol should not be used to remove the hexachlorophene. Care should be taken to prevent hexachlorophene from entering the palpebral fissure because it is injurious to the corneal epithelium.[7]

It has been noted that benzylkonium chloride is incompatible with iodine and therefore should not be placed in direct contact with it, even on skin.[8] In addition, benzylkonium chloride is inactivated by blood, other organic material, soap, and cotton material which often is used in its application. Ophthalmologists who use multiple agents should reconsider their individual activity with regard to effectiveness, spectrum, and duration of action to avoid overlap.

Some doubt exists as to the efficacy of any preoperative chemical preparation of the eye. Lincoff and coworkers found in one study that an extensive preoperative ophthalmic preparation, including three preoperative soap scrubs, povidone-iodine preparation, saline lavage, and bathing and lavaging implants with chloramphenicol, did not significantly alter their rate of infected scleral implants.[9] In a later study, Hahn, Lincoff, Lincoff, and Kreissig determined that the same organism found on routine intraoperative conjunctival culture was usually the infecting agent in infected scleral implants.[10] They felt that the source of infection was contamination at the site of the buckle operation. Perhaps more emphasis should be placed on sterilization of the conjunctiva. Sterilization of the conjunctiva ultimately might decrease the incidence of infectious endophthalmitis.

REFERENCES

1 Eberth C. *Virchows Arch.*, Bd 52, 1875. As quoted in Wheeler ES. The development of antiseptic surgery. *Am J Surg* 1974; 127:573-579.

2 Maumenee AE, Michler RC. Sterility of the operative field after ocular surgery. *Trans Pacific Coast Otōōphthalmol Soc* 1951; 32:172-179.

3 Kiffney GT Jr, Hattaway AC. Povidone-iodine as an ophthalmic antiseptic. *Surg Forum* 1966; 17:434-436.

4 Chase RC, Ellis PP. Iodophosphors and skin asepsis. *Ann Ophthalmol* 1970; 12:312-317.

5 Saggers BA, Stewart GT. Polyvinylpyrrolidone-iodine: an assessment of anti-bacterial activity. *J Hyg* (Camb) 1964; 62:509-518.

6 Fahmy JA. Bacterial flora in relation to cataract extraction. V. Effects of topical antibiotics on the preoperative conjunctival flora. *Acta Ophthalmol* 1980; 58:567-575.

7 Browning CW, Lippas J. pHisoHex keratitis. *Arch Ophthalmol* 1955; 53:817-824.

8 *Physician's Desk Reference*, ed 7. Oradell, Medical Economics Co., 1980, p 1859.

9 Lincoff H, Nadel A, O'Connor P. The changing character of the infected scleral implant. *Arch Ophthalmol* 1970; 84:421-426.

10 Hahn YS, Lincoff A, Lincoff H, et al. Infection after sponge implantation for scleral buckling. *Am J Ophthalmol* 1979; 87:180-185.

A. INGREDIENT NAME:

THYMOL IODIDE

B. Chemical Name:

Dithymol Diiodide, Iodothymol

C. Common Name:

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

	(Specifications)	*(Results)*
Assay:	43.0% min.	44.08%

E. Information about how the ingredient is supplied:

Reddish-brown, tasteless powder

F. Information about recognition of the substance in foreign pharmacopeias:

Port. and Swiss.

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

H. Information about dosage forms used:

It has been used in dusting powders and ointments, and in dental root filling.

I. Information about strength:

J. Information about route of administration:

K. Stability data:

Stable
Loses iodine on prolonged exposure to light.
Gives off purple iodine vapors when heated above 100°

L. Formulations:

M. Miscellaneous Information:

CERTIFICATE OF ANALYSIS

30-1240
#4776

PRODUCT: THYMOL IODIDE POWDER. GRADE: PURIFIED
RELEASE #: 102161 LOT # :B60244A02 CODE:MT15545

		SPECIFICATIONS	RESULT
1.	DESCRIPTION	REDDISH BROWN POWDER	CONFORMS
2.	Identification	To pass test	Passes test
3.	Alkalinity	To pass test	Passes test
4.	Soluble Halides	1.5% max.	0.9%
5.	Assay	43.0% min.	44.08%
6.	Solubility	To pass tests	Passes tests
7.	Loss on drying (4 hrs./sulfuric acid)	3% max.	0.2%

ATTENTION: TONY HATCHETT

Date :02/13/97 Prepared by: J.PATEL

10592 Approved by: 2/97

QUALITY CONTROL REPORT

CHEMICAL NAME.: THYMOL IODIDE PURIFIED _____

MANUFACTURE LOT NO.: B62871M05

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: USP__/BP__/NF__/MERCK__/MART.__/CO.SPECS.__.

1) DESCRIPTION.:
REDDISH-BROWN OR REDDISH-YELLOW, BULKY POWDER; SLIGHT AROMATIC ODOR; LOSES IODINE ON PROLONGED EXPOSURE TO LIGHT.

2) SOLUBILITY.:
INSOLUBLE IN WATER, GLYCEROL, ALKALINE SOLUTIONS; READILY SOLUBLE IN CHLOROFORM, ETHER, COLLODION, FIXED AND VOLATILE OILS, USUALLY LEAVING A SLIGHT RESIDUE; SLIGHTLY SOLUBLE IN ALCOHOL.

3) MELTING POINT.:
GIVES OFF PURPLE IODINE VAPORS WHEN HEATED ABOVE 100 DEGREES.

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:

PASSES.: _____ **FAILS.:** _____

COMMENTS.:

ANALYST SIGNATURE.: _____ **DATE.:** _____

PREPACK TEST.: _____ **DATE.:** _____ **INITIAL.:** _____

RETEST.: _____ **DATE.:** _____ **INITIAL.:** _____

---------- IDENTIFICATION ----------

PRODUCT #: T2763 NAME: THYMOL IODIDE

CAS #: 552-22-7

---------- TOXICITY HAZARDS ----------

DATA NOT AVAILABLE

---------- HEALTH HAZARD DATA ----------

ACUTE EFFECTS

MAY BE HARMFUL BY INHALATION, INGESTION, OR SKIN ABSORPTION.

MAY CAUSE IRRITATION.

THE TOXICOLOGICAL PROPERTIES HAVE NOT BEEN THOROUGHLY INVESTIGATED.

FIRST AID

IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS CONSCIOUS.

CALL A PHYSICIAN.

IN CASE OF SKIN CONTACT, FLUSH WITH COPIOUS AMOUNTS OF WATER FOR AT LEAST 15 MINUTES. REMOVE CONTAMINATED CLOTHING AND SHOES. CALL A PHYSICIAN.

IF INHALED, REMOVE TO FRESH AIR. IF BREATHING BECOMES DIFFICULT, CALL A PHYSICIAN.

IN CASE OF CONTACT WITH EYES, FLUSH WITH COPIOUS AMOUNTS OF WATER FOR AT LEAST 15 MINUTES. ASSURE ADEQUATE FLUSHING BY SEPARATING THE EYELIDS WITH FINGERS. CALL A PHYSICIAN.

---------- PHYSICAL DATA ----------

APPEARANCE AND ODOR

POWDER

---------- FIRE AND EXPLOSION HAZARD DATA ----------

EXTINGUISHING MEDIA

WATER SPRAY.

CARBON DIOXIDE, DRY CHEMICAL POWDER OR APPROPRIATE FOAM.

SPECIAL FIREFIGHTING PROCEDURES

WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING TO PREVENT CONTACT WITH SKIN AND EYES.

UNUSUAL FIRE AND EXPLOSIONS HAZARDS

EMITS TOXIC FUMES UNDER FIRE CONDITIONS.

---------- REACTIVITY DATA ----------

STABILITY

STABLE.

HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS

CARBON MONOXIDE, CARBON DIOXIDE

HAZARDOUS POLYMERIZATION
WILL NOT OCCUR.
---------- SPILL OR LEAK PROCEDURES ----------
STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED
WEAR PROTECTIVE EQUIPMENT.
SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL.
AVOID RAISING DUST.
VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS COMPLETE.
WASTE DISPOSAL METHOD
DISSOLVE OR MIX THE MATERIAL WITH A COMBUSTIBLE SOLVENT AND BURN IN A
CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER.

OBSERVE ALL FEDERAL, STATE, AND LOCAL LAWS.
--- PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE ---
WEAR APPROPRIATE NIOSH/MSHA-APPROVED RESPIRATOR, CHEMICAL-RESISTANT
GLOVES, SAFETY GOGGLES, OTHER PROTECTIVE CLOTHING.
MECHANICAL EXHAUST REQUIRED.
CAUTION:
AVOID CONTACT AND INHALATION.
THE ABOVE INFORMATION IS BELIEVED TO BE CORRECT BUT DOES NOT PURPORT TO BE
ALL INCLUSIVE AND SHALL BE USED ONLY AS A GUIDE. SIGMA ALDRICH SHALL NOT BE
HELD LIABLE FOR ANY DAMAGE RESULTING FROM HANDLING OR FROM CONTACT WITH THE
ABOVE PRODUCT. SEE REVERSE SIDE OF INVOICE OR PACKING SLIP FOR ADDITIONAL
TERMS AND CONDITIONS OF SALE

of fungous skin infections.

Thymol (0.01%) is added as an antoxidant to halothane, trichloroethylene, and tetrachloroethylene. Thymol, 10% in isopropyl alcohol, has been used to preserve urine.

Thymol had only a low solubility in water and was a poor bactericide. Its use as a disinfectant even for clinical thermometers was not recommended.—Report by the Public Health Laboratory Service Committee on the Testing and Evaluation of Disinfectants, *Br. med. J.*, 1965, *1*, 408.

Herpes. Fifteen patients with herpes of the genitalia were treated topically with thymol (as Listerine) twice daily. Symptomatic relief was obtained in 14 days with gradual healing of the lesions. There had been one recurrence in 8 months.— H. M. Radman, *Md St. med. J.*, 1978, *27*, 49. See also V. Knight and M. W. Noall (letter), *New Engl. J. Med.*, 1976, *294*, 337.

Use in food. The Food Additives and Contaminants Committee recommended that, on the grounds of safety, thymol could continue to be used as a stabiliser for solvents used in food.— *Report on the Review of Solvents in Food*, FAC/REP/25, Ministry of Agriculture, Fisheries and Food, London, HM Stationery Office, 1978.

Preparations

Compound Thymol Glycerin *(B.P.)*. Glycerinum Thymolis Compositum. Thymol 50 mg, sodium bicarbonate 1 g, borax 2 g, sodium benzoate 800 mg, sodium salicylate 520 mg, menthol 30 mg, cineole 0.13 ml, pumilio pine oil 0.05 ml, methyl salicylate 0.03 ml, alcohol (90%) (or industrial methylated spirit, suitably diluted) 2.5 ml, glycerol 10 ml, sodium metabisulphite 35 mg, carmine, food grade of commerce, 30 mg, dilute ammonia solution 0.075 ml, water to 100 ml. pH 7.1 to 7.6. To be diluted with about 3 times its vol. of warm water before use; diluted solutions should be prepared immediately fore use.

odified formula. Fading and discoloration of Compound Thymol Glycerin during storage could be minimised by increasing the sodium metabisulphite to 50 mg per 100 ml and by protecting from light.—Pharm. Soc. Lab. Rep. No. P/69/33, 1969.

Reports of contamination of Compound Thymol Glycerin.— M. H. Hughes (letter), *Lancet*, 1972, *1*, 210; T. A. Rees (letter), *ibid.*, 532.

A study suggesting that phenol might be worth investigating as a potential preservative of Compound Thymol Glycerin.— Pharm. Soc. Lab. Rep. P/78/9, 1978. Confirmation that phenol 0.5% was physically compatible with Compound Thymol Glycerin. Initial studies also suggested that cinnamon oil and citral appeared worthy of further investigation as preservatives.— Pharm. Soc. Lab. Rep. P/80/3, 1980.

Compound Thymol Mouth-wash *(B.P.C. 1949)*. Collut. Thymol. Co. Thymol 30 mg, liquefied phenol 0.52 ml, potassium hydroxide solution 0.52 ml, methyl salicylate 0.01 ml, peppermint oil 0.01 ml, bordeaux B solution 1.04 ml, water to 100 ml. To be diluted with 3 times its vol. of warm water before use.

Amended formula. Thymol 30 mg, liquefied phenol 0.52 ml, potassium hydroxide solution 0.52 ml, methyl salicylate 0.01 ml, peppermint oil 0.01 ml, amaranth solution 1 ml, water to 100 ml.—*Compendium of Past Formulae 1933 to 1966*, London, The National Pharmaceutical Union, 1969.

Compound Thymol Solution-tablets *(B.P.C. 1963)*. Solv. Thymol. Co. Each contains thymol 3.24 mg, sodium bicarbonate 324 mg, borax 324 mg, phenol 32.4 mg, and amaranth 650 µg. One solution-tablet to be dissolved in 60 ml of warm water.

Thymol Mouth-wash Compound *(A.P.F.)*. Collut. Thymol. Alb.; Liq. Thymol. Co. Thymol 150 mg, menthol 50 mg, benzoic acid 800 mg, methyl salicylate 0.05 ml, cineole 0.05 ml, glycerol 2 ml, alcohol (90%) 20 ml, water to 100 ml. Dilute with 7 vol. of water for use as a gargle or mouth-wash.

2292-l

Dithymol Di-iodide. 4,4'-Bis(iodo-oxy)-5,5'-di-isopropyl-2,2'-dimethyl-1,1'-biphenyl.
$C_{20}H_{24}I_2O_2 = 550.2$.

CAS — 552-22-7.

2283-e

Thymol Iodide *(B.P.C. 1949)*. Dithymol Diiodide; Iodothymol; Timol Ioduro. A mixture of iodine derivatives of thymol, chiefly dithymol di-iodide, containing not less than 43% of iodine.

NOTE. The name iodothymol is also applied to an anthelmintic compound (see p.94).

Pharmacopoeias. In *Port.* and *Swiss.*

A reddish-brown or buff-coloured, almost tasteless, bulky, amorphous powder with a slight aromatic odour. Practically **insoluble** in water, glycerol, and sodium hydroxide solution; slightly soluble in alcohol; soluble in chloroform, ether, soft paraffin, and fixed and volatile oils, usually leaving a slight residue. **Incompatible** with alkalis, mercuric chloride, and metallic oxides. **Protect** from light.

Thymol iodide is insoluble and has little or no antiseptic action but acts as an absorbent and protective. It has been used in dusting-powders and ointments, and in dental root filling preparations.

2284-l

Tribromometacresol. 2,4,6-Tribromo-*m*-cresol; 2,4,6-Tribromo-3-methylphenol.
$C_7H_5Br_3O = 344.8$.

CAS — 4619-74-3.

Tribromometacresol is an antifungal agent used in the treatment of dermatomycoses. It is applied topically as an aerosol spray containing 2%. It should be applied with caution to suppurating mycoses; it should not be applied near the eyes or mucous membranes.

Proprietary Names
Triphysan *(Dumex, Denm.)*; Tri-Physol *(Sigma, Austral.)*.

2285-y

Triclobisonium Chloride. Hexamethylenebis{dimethyl[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]ammonium chloride}.
$C_{36}H_{74}Cl_2N_2 = 605.9$.

CAS — 7187-64-6 (triclobisonium); 79-90-3 (chloride).

A white or nearly white, almost odourless, crystalline powder. M.p. about 243°. Freely **soluble** in water, alcohol, and chloroform; practically insoluble in ether. **Protect** from light.

Triclobisonium chloride is a quaternary ammonium compound with properties and uses similar to those of other cationic surfactants as described under Cetrimide, p.551. It has been reported to have activity against *Candida albicans* and *Trichomonas vaginalis*. It has been applied topically as a 0.1% ointment or cream in the treatment of skin infections and as a 0.1% cream or pessaries in the treatment of vaginitis.

2286-j

Triclocarban. 3,4,4'-Trichlorocarbanilide. 1-(4-Chlorophenyl)-3-(3,4-dichlorophenyl)urea.
$C_{13}H_9Cl_3N_2O = 315.6$.

CAS — 101-20-2.

A fine white odourless powder. M.p. 250° to 256°. Practically **insoluble** in water; soluble 1 in 25 of acetone, 1 in 100 of propylene glycol, and 1 in 100 of dimethyl phthalate; soluble 1 in 10 to 1 in 4 of macrogols.

Macrogol 400 monolaurate increased the solubility of triclocarban, resulting in increased bactericidal activity.— A. E. Elkhouly and R. C. S. Woodroffe, *J. appl Bact.*, 1973, *36*, 387.

Adverse Effects and Precautions. When subjected to prolonged high temperatures triclocarban can decompose to form toxic chloroanilines, which can be absorbed through the skin.

Mild photosensitivity has been seen in patch testing.

An outbreak of methaemoglobinaemia in 18 infants (12 premature) in a nursery in a 5-week period ceased when the laundry process applied to clothing and napkins was revised. The process had involved washing in detergent, blueing, a chemical rinse containing triclocarban 2%, neutralising, drying and autoclaving. — R. O. Fisch *et al.*, *J. Am. med. Ass.*, 1963, *185*, 760.

Eight patients developed methaemoglobinaemia after receiving an enema prepared from soap containing about 2% of triclocarban. Three days prior to the incident the procedure for preparing the soap gel had been changed to include heating near to boiling-point for several hours. Laboratory tests showed that boiling reduced the triclocarban content of the soap gel (*p*H 9.5) and led to the formation of primary amines.— R. R. Johnson *et al.*, *Pediatrics*, 1963, *31*, 222.

Cutaneous and mucosal lesions.— H. Barrière, *Therapeutique*, 1973, *49*, 685.

Uses. Triclocarban is a non-phenolic disinfectant. It is bacteriostatic against Gram-positive organisms in high dilutions but is less effective against Gram-negative organisms and some fungi. It is used in soaps, usually in a concentration of 2%, for similar purposes to hexachlorophane, and has been applied in solutions, powders, and ointments for the control of skin infections.

A review of antimicrobial agents, including triclocarban, used in cosmetics.— I. R. Gucklhorn, *Mfg Chem.*, 1970, *41* (Feb.), 30.

Proprietary Preparations

Cutisan *(Martindale Pharmaceuticals, UK; Farillon, UK)*. Triclocarban, available as **Ointment** containing 2%; as **Powder** containing 1%; and as **Solution** containing 1%. For infected skin conditions, leg ulcers, and burns. (Also available as Cutisan in *Fr.*).

TCC *(Monsanto, UK)*. A brand of triclocarban.

Other Proprietary Names

Arg.—Ungel; *Belg.*—Solubacter; *Fr.*—Nobacter, Septivon-Lavril, Solubacter.

A preparation containing triclocarban was also formerly marketed in Great Britain under the proprietary name Crinagen (*Pharmax*).

2287-z

Triclosan. Cloxifenol; CH 3565. 5-Chloro-2-(2,4-dichlorophenoxy)phenol.
$C_{12}H_7Cl_3O_2 = 289.5$.

CAS — 3380-34-5.

A white to off-white crystalline powder or soft agglomerates with a slightly aromatic odour. M.p. 55° to 57°. Practically **insoluble** in water; very soluble in most organic solvents; soluble 1 in 3 of 4% sodium hydroxide solution. **Protect** from light.

Adverse Effects. Contact dermatitis has occasionally been reported.

From studies on the percutaneous absorption of triclosan in *rats*, it was calculated that the absorbed dose from a shampoo preparation (0.05% triclosan) in a woman would be about 4.8 µg per kg body-weight and from an aerosol (0.1% triclosan) 24.9 µg per kg. These doses were considered to have no effect in humans.— J. G. Black and D. Howes, *J. Soc. cosmet. Chem.*, 1975, *26*, 205.

Uses. Triclosan is bacteriostatic against Gram-positive and most Gram-negative organisms. It has little activity against *Pseudomonas* spp., yeasts, or fungi. It is used in surgical scrubs, soaps, and deodorants in concentrations of 0.05 to 2%.

Review of properties and microbiological activity.— T. E. Furia and A. G. Schenkel, *Soap chem. Spec.*, 1968, *44* (Jan.), 47.

Handwashing for 2 minutes with soap containing triclosan 0.75% was less effective in removing skin bacteria than washing with soap containing hexachlorophane 2%.

'otatory, but the angle of rotation in a

yme Oil is not less than 1.4950 and not

'me Oil with 10 ml. of hot water, and
moistened filter: not even a transient
te upon the addition of 1 drop of ferric

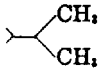
Oil into a cassia flask, add 75 ml. of
tightly, shake the mixture thoroughly,
cient potassium hydroxide T.S. to raise
e graduated portion of the neck of the
me clear, adjust it to the temperature
volume of the residual liquid. This
ıe presence of not less than 40 per cent,

in tight, light-resistant containers.

y $1^1/_2$ minims).

OL

H



Mol. wt. 150.22

tals, often large, or as a white, crystal-
-like odor and a pungent taste. It is
nsity than water, but when liquefied by
ol solution is neutral to litmus.
about 1000 ml. of water, in 1 ml. of
f ether, and in about 2 ml. of olive oil.
l or volatile oils.

l weight of camphor or menthol: the

l in 1 ml. of glacial acetic acid, and add
f nitric acid: the liquid shows a deep
flected light.
tube in a water bath with 5 ml. of a 10
: a clear, colorless, or pale red solution
n standing, without the separation of
ew drops of chloroform to this solution
t color is produced.
ıd 51°, but when melted remains liquid
391.

Non-volatile residue—Volatilize about 2 Gm. of Thymol, accurately weighed, on a water bath, and dry at 100° to constant weight: not more than 0.05 per cent of residue remains.

Packaging and storage—Preserve Thymol in tight, light-resistant containers.

CATEGORY—Antifungal; antibacterial; anthelmintic.

USUAL DOSE—Anthelmintic, **2 Gm.** (approximately 30 grains) divided into three doses.

Thymol Iodide

THYMOL IODIDE

Thymol Iodide is a mixture of iodine derivatives of thymol, principally dithymol diiodide $[C_6H_2(CH_3)(OI)(C_3H_7)\text{-}1,3,4]_2$, containing, when dried over sulfuric acid for 4 hours, not less than 43 per cent of I.

Description—Thymol Iodide occurs as a reddish brown or reddish yellow, bulky powder, with a very slight, aromatic odor. It is affected by light.

Solubility—Thymol Iodide is freely soluble in chloroform, in ether, in collodion, and in fixed and volatile oils, usually leaving a slight residue. It is slightly soluble in alcohol. Thymol Iodide is insoluble in water and in glycerin, and in cold and in hot solutions of the fixed alkali hydroxides.

Identification—Heat about 100 mg. of Thymol Iodide with 2 ml. of sulfuric acid: it decomposes with the separation of iodine.

Loss on drying—Dry Thymol Iodide over sulfuric acid for 4 hours: it loses not more than 2 per cent of its weight, page 690.

Residue on ignition—Thymol Iodide yields not more than 1.5 per cent of residue on ignition, page 711.

Soluble halides—Digest 100 mg. of Thymol Iodide with 50 ml. of warm water for 10 minutes, filter, cool, and add 5 drops of diluted nitric acid and 1 ml. of silver nitrate T.S.: any turbidity produced is not greater than that in a control test containing 2 mg. of potassium iodide.

Alkalinity—Shake 500 mg. of Thymol Iodide with 10 ml. of water, and filter the mixture: the filtrate is not alkaline to litmus.

Iodine—Shake 500 mg. of Thymol Iodide with 10 ml. of water, filter the mixture, and add a few drops of starch T.S.: no blue color is produced.

Assay—Mix thoroughly about 250 mg. of Thymol Iodide, previously dried over sulfuric acid for 4 hours and accurately weighed, with about 3 Gm. of anhydrous potassium carbonate. Place the mixture in a platinum crucible, cover with about 1 Gm. of anhydrous potassium carbonate, and heat moderately, gradually increasing the heat but not exceeding a dull redness, until the mass is completely carbonized. Extract the residue with boiling water until the last washing, after acidification with diluted nitric acid, produces no opalescence with silver nitrate T.S. Heat the combined washings, which measure about 150 ml., on a water bath, and add a solution of potassium permanganate (1 in 20) in small portions, until the hot liquid remains pink. Add just enough alcohol to remove the pink tint, cool to room temperature, dilute to exactly 200 ml., mix well, and filter through a dry filter, rejecting the first 50 ml. of filtrate. To exactly 100 ml. of the subsequent clear filtrate, add about 1 Gm. of potassium iodide (free from iodate) and an excess of diluted sulfuric acid, and titrate the liberated iodine with 0.1 *N* sodium thiosulfate, adding starch T.S. near the end of the titration. Each ml. of 0.1 *N* sodium thiosulfate is equivalent to 2.115 mg. of I.

Packaging and storage—Preserve Thymol Iodide in tight, light-resistant containers.

CATEGORY—Antifungal; anti-infective.

MSDS Material Safety Data Sheet
Professional Compounding Centers of America
9901 South Wilcrest, Houston Texas 77099 1-800-331-2498

24 Hour Chemtrec Phone 1-800-424-9300

---------- IDENTIFICATION ----------

PRODUCT #: 30-1240 NAME: THYMOL IODIDE
CAS #: 552-22-7

---------- TOXICITY HAZARDS ----------

DATA NOT AVAILABLE

---------- HEALTH HAZARD DATA ----------

ACUTE EFFECTS

MAY BE HARMFUL BY INHALATION, INGESTION, OR SKIN ABSORPTION.
MAY CAUSE IRRITATION.
THE TOXICOLOGICAL PROPERTIES HAVE NOT BEEN THOROUGHLY INVESTIGATED.

FIRST AID

IF SWALLOWED, WASH OUT MOUTH WITH WATER
PROVIDED PERSON IS CONSCIOUS.
CALL A PHYSICIAN.
IN CASE OF SKIN CONTACT, FLUSH WITH COPIOUS AMOUNTS OF WATER FOR AT LEAST 15 MINUTES. REMOVE CONTAMINATED CLOTHING AND SHOES. CALL A PHYSICIAN.
IF INHALED, REMOVE TO FRESH AIR. IF BREATHING BECOMES DIFFICULT, CALL A PHYSICIAN.
IN CASE OF CONTACT WITH EYES, FLUSH WITH COPIOUS AMOUNTS OF WATER FOR AT LEAST 15 MINUTES. ASSURE ADEQUATE FLUSHING BY SEPARATING THE EYELIDS WITH FINGERS. CALL A PHYSICIAN.

---------- PHYSICAL DATA ----------

APPEARANCE AND ODOR: POWDER

---------- FIRE AND EXPLOSION HAZARD DATA ----------

EXTINGUISHING MEDIA

WATER SPRAY.
CARBON DIOXIDE, DRY CHEMICAL POWDER OR APPROPRIATE FOAM.

SPECIAL FIREFIGHTING PROCEDURES

WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING TO PREVENT CONTACT WITH SKIN AND EYES.

UNUSUAL FIRE AND EXPLOSIONS HAZARDS

EMITS TOXIC FUMES UNDER FIRE CONDITIONS.

---------- REACTIVITY DATA ----------

STABILITY

STABLE. K

HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS

CARBON MONOXIDE, CARBON DIOXIDE

HAZARDOUS POLYMERIZATION WILL NOT OCCUR.

---------- SPILL OR LEAK PROCEDURES ----------

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED
WEAR PROTECTIVE EQUIPMENT.
SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL.
AVOID RAISING DUST.
VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS COMPLETE.

WASTE DISPOSAL METHOD
DISSOLVE OR MIX THE MATERIAL WITH A COMBUSTIBLE SOLVENT AND BURN IN A CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER.
OBSERVE ALL FEDERAL, STATE, AND LOCAL LAWS.

--- PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE ---
WEAR APPROPRIATE NIOSH/MSHA-APPROVED RESPIRATOR, CHEMICAL-RESISTANT GLOVES, SAFETY GOGGLES, OTHER PROTECTIVE CLOTHING.
MECHANICAL EXHAUST REQUIRED.
CAUTION:
AVOID CONTACT AND INHALATION.

THE ABOVE INFORMATION ON THIS MSDS WAS OBTAINED FROM CURRENT AND REPUTABLE SOURCES. HOWEVER THE DATA IS PROVIDED WITHOUT WARRANTY, EXPRESSED OR IMPLIED, REGARDLESS OF ITS CORRECTNESS OR ACCURACY. IT IS THE USER'S RESPONSIBILITY BOTH TO DETERMINE SAFE CONDITIONS FOR USE OF THIS PRODUCT AND TO ASSUME LIABILITY FOR LOSS, INJURY, DAMAGE OR EXPENSE RESULTING FROM IMPROPER USE OF THIS PRODUCT.

A. INGREDIENT NAME:

TINIDAZOLE

B. Chemical Name:

1-(2-ethylsuphonylethyl)-2-methyl-5-nitroimidazole

C. Common Name:

Fasigin

D. Chemical grade or description of the strength, quality, and purity of the ingredient:

Assay: 99.36% dry basis

E. Information about how the ingredient is supplied:

An almost white or pale yellow, crystalline powder, odorless.

F. Information about recognition of the substance in foreign pharmacopeias:

British Pharmacopeia 1993

G. Bibliography of available safety and efficacy data including peer reviewed medical literature:

Ripa, T. The plasma half-life was about 13 hours. *Chemotheraapy, Basle,* 1977; 14: 1084.

Jokipii, A. M. M Concentrations in the CSF. *J antimicrob. Chemother.,* 1977; 3: 239.

Sawyer, P. R. A review of tinidazole in the treatment of trichomoniasis, amoebiasis, and giardiasis. *Drugs,* 1976; 11: 423.

Wüst, J. Figures achieved with metronidazole and ornidazole. *Antimicrob, Ag Chemother.* 1977; 11: 631.

Wise, R. The median minimum inhibitory concentration of tinidazole against Bacteroides. *Chemotherapy, Basle,* 1977; 23: 19.

Klastersky, J. The activities of clindamycin, tinidazole, an doxycycline in vitro. *Antimicrob. Ag. Chemother.,* 1977; 12: 563.

Bakshi, J. S. Amoebiasis. *Drugs,* 1978; 15(Suppl): 1, 33.

Apte, V. V. and Packard, R. S. Excellent response was achieved in patients with trichomonal vaginitis. *Drugs,* 1978; 15(Suppl 1): 43.

Welch, J. S. A single doe of tinidazole was as effective as the longer regimen. *Med J Aust.,* 1978; 1: 469.

Levi, G. C. A cure-rate in patients with giardiasis treated with tinidazole. *Am J trop Med. Hyg.* 1977; 26: 564.

Anjaneyulu, R. Trichomoniasis. *J int. med Res.,* 1977; 5: 438.

H. Information about dosage forms used:

Capsules

I. Information about strength:

150mg twice a day

J. Information about route of administration:

Orally

K. Stability data:

Manufacture Date: June 1997
Expiration Date: June 2002
Store in a well-closed container, protected from light.

L. Formulations:

M. Miscellaneous Information:

30-2391
54235

ANALYSIS CERTIFICATE No. 3203

Your Ord. No. - 8th October 1997 Our Ref. No. 2905

MATERIAL TINIDAZOLE JP 12 1-[2-(ethylsulfonyl)-ethyl]-2-methyl-5-nitroimidazole	Quantity	Batch
	Kg. 10.-	75179

Empirical formula	$C_8H_{13}N_2O_4S$	Specific rotation	
Molecular weight	247.28		
Aspect	crystalline powder	Light absorption	
Color	creamish		
Odor	characteristic odour	Loss on drying	0.2565%
Taste		Residue on ignition	0.046%
Melting point	126.1°C	Chloride	
Boiling range		Sulfate	
Solubility	conforms	Heavy metals	max. 10 ppm
		Identification:	positive.
pH			

Titer (Assay) 99.36% dry basis

Other requirements, notes Related substances by TLC : passes.

Bulk density : 0.6502 gm/u

MANUF. DATE : JUNE 1997
EXPIRY DATE : JUNE 2002

The Analyst

11/97

QUALITY CONTROL REPORT

CHEMICAL NAME.: TINIDAZOLE

MANUFACTURE LOT NO.: 77405

PHYSICAL TEST

SPECIFICATION TEST STANDARD.: *USP__/BP__/MERCK__/NF__/MART.__/CO.SPECS.__.*

1) DESCRIPTION.:
PALE YELLOW FINE CRYSTALLINE POWDER; ODORLESS.

2) SOLUBILITY.:
SPARINGLY SOLUBLE IN WATER AND IN ALCOHOL; SOLUBLE IN DILUTE ACIDS.

3) MELTING POINT.:
MELTS AT ABOUT 126-127 degree.

4) SPECIFIC GRAVITY.:

5) IDENTIFICATION.:
A) COMPLIES (A) AS PER IR SPECTRUM CO.SPECS.

PASSES.: _____ **FAILS.:** _____

COMMENTS.:

ANALYST SIGNATURE.: _____ **DATE.:** _____

PREPACK TEST.: _____ **DATE.:** _____ **INITIAL.:** _____

RETEST.: _____ **DATE.:** _____ **INITIAL.:** _____

---------- IDENTIFICATION ----------

PRODUCT #: T3021 NAME: TINIDAZOLE

CAS #: 19387-91-8

MF: C8H13N3O4S1

SYNONYMS

BIOSHIK * CP 12574 * 1-(2-(ETHYLSULFONYL)-ETHYL)-2-METHYL-5-NITROIMIDAZOLE * FASIGIN * FASIGYN * 1H-IMIDAZOLE, 1-(2-(ETHYLSULFONYL)ETHYL)-2-METHYL-5-NITRO- * PLETIL * SIMPLOTAN * SORQUETAN * TINIDAZOL * TINIDAZOLE * TRICOLAM * TRIMONASE *

---------- TOXICITY HAZARDS ----------

RTECS NO: NI6255000

IMIDAZOLE, 1-(2-(ETHYLSULFONYL)ETHYL)-2-METHYL-5-NITRO-

TOXICITY DATA

ORL-RAT LD50:2710 MG/KG	IYKEDH 11,811,80
IPR-RAT LD50:2720 MG/KG	IYKEDH 11,811,80
SCU-RAT LD50:3000 MG/KG	IYKEDH 11,811,80
IVN-RAT LD50:>250 MG/KG	YKYUA6 32,204,81
ORL-MUS LD50:3200 MG/KG	JMCMAR 21,781,78
IPR-MUS LD50:2730 MG/KG	IYKEDH 11,811,80
SCU-MUS LD50:3940 MG/KG	IYKEDH 11,811,80
IVN-MUS LD50:>250 MG/KG	YKYUA6 32,204,81

TARGET ORGAN DATA

BEHAVIORAL (SOMNOLENCE)

BEHAVIORAL (CONVULSIONS OR EFFECT ON SEIZURE THRESHOLD)

LUNGS, THORAX OR RESPIRATION (CYANOSIS)

ONLY SELECTED REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES (RTECS)

DATA IS PRESENTED HERE. SEE ACTUAL ENTRY IN RTECS FOR COMPLETE INFORMATION.

---------- HEALTH HAZARD DATA ----------

ACUTE EFFECTS

HARMFUL IF SWALLOWED, INHALED, OR ABSORBED THROUGH SKIN.

EXPOSURE CAN CAUSE:

GASTROINTESTINAL DISTURBANCES

NAUSEA, HEADACHE AND VOMITING

URTICARIA, FLUSHING, PRURITUS, DYSURIA, CYSTITIS, DRYNESS OF THE MOUTH,

DIZZINESS, VERTIGO, AND VERY RARELY, INCOORDINATION AND ATAXIA,

A METALLIC, SHARP, UNPLEASANT TASTE, FURRY TONGUE, GLOSSITIS, AND STOMATITIS.

EXPOSURE TO AND/OR CONSUMPTION OF ALCOHOL

MAY INCREASE TOXIC EFFECTS.

CHRONIC EFFECTS

POSSIBLE CARCINOGEN.

POSSIBLE MUTAGEN.
FIRST AID
IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS CONSCIOUS.
CALL A PHYSICIAN.
IN CASE OF SKIN CONTACT, FLUSH WITH COPIOUS AMOUNTS OF WATER

FOR AT LEAST 15 MINUTES. REMOVE CONTAMINATED CLOTHING AND

SHOES. CALL A PHYSICIAN.
IF INHALED, REMOVE TO FRESH AIR. IF BREATHING BECOMES DIFFICULT, CALL A PHYSICIAN.
IN CASE OF CONTACT WITH EYES, FLUSH WITH COPIOUS AMOUNTS OF WATER

FOR AT LEAST 15 MINUTES. ASSURE ADEQUATE FLUSHING BY SEPARATING

THE EYELIDS WITH FINGERS. CALL A PHYSICIAN.
---------- PHYSICAL DATA ----------
MELTING PT: 127-128'C
SOLUBILITY: CHLOROFORM-SOLUBLE
APPEARANCE AND ODOR
SOLID.
---------- FIRE AND EXPLOSION HAZARD DATA ----------
EXTINGUISHING MEDIA
CARBON DIOXIDE, DRY CHEMICAL POWDER OR APPROPRIATE FOAM.
SPECIAL FIREFIGHTING PROCEDURES
WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING TO
PREVENT CONTACT WITH SKIN AND EYES.
---------- REACTIVITY DATA ----------
STABILITY
STABLE.
HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS
THERMAL DECOMPOSITION MAY PRODUCE CARBON MONOXIDE, CARBON DIOXIDE,
AND NITROGEN OXIDES.
HAZARDOUS POLYMERIZATION
WILL NOT OCCUR.
---------- SPILL OR LEAK PROCEDURES ----------
STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED
WEAR SELF-CONTAINED BREATHING APPARATUS, RUBBER BOOTS AND HEAVY

RUBBER GLOVES.
SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL.
AVOID RAISING DUST.

VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS COMPLETE.

WASTE DISPOSAL METHOD

DISSOLVE OR MIX THE MATERIAL WITH A COMBUSTIBLE SOLVENT AND BURN IN A
CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER.

OBSERVE ALL FEDERAL, STATE, AND LOCAL LAWS.

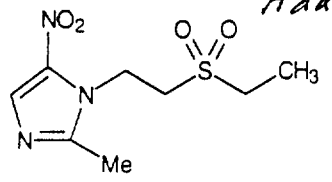
--- PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE ---

NIOSH/MSHA-APPROVED RESPIRATOR.
USE ONLY IN A CHEMICAL FUME HOOD.
COMPATIBLE CHEMICAL-RESISTANT GLOVES.
CHEMICAL SAFETY GOGGLES.
HARMFUL BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.

POSSIBLE RISK OF IRREVERSIBLE EFFECTS.
WEAR SUITABLE PROTECTIVE CLOTHING.
DO NOT BREATHE DUST.
POSSIBLE CARCINOGEN.
POSSIBLE MUTAGEN.

THE ABOVE INFORMATION IS BELIEVED TO BE CORRECT BUT DOES NOT PURPORT TO BE
ALL INCLUSIVE AND SHALL BE USED ONLY AS A GUIDE. SIGMA ALDRICH SHALL NOT BE
HELD LIABLE FOR ANY DAMAGE RESULTING FROM HANDLING OR FROM CONTACT WITH THE
ABOVE PRODUCT. SEE REVERSE SIDE OF INVOICE OR PACKING SLIP FOR ADDITIONAL
TERMS AND CONDITIONS OF SALE

Tinidazole ☆



$C_8H_{13}N_3O_4S$ 247.3 *19387-91-8*

Definition Tinidazole contains not less than 98.0% and not more than 101.0% of 1-(2-ethylsulphonylethyl)-2-methyl-5-nitroimidazole, $C_8H_{13}N_2O_4S$, calculated with reference to the dried substance.

Characteristics An almost white or pale yellow, crystalline powder; practically insoluble in *water*; soluble in *acetone* and in *dichloromethane*; sparingly soluble in *methanol*.

Identification *Identification test C may be omitted if identification tests A, B, D and E are carried out. Identification tests B, D and E may be omitted if identification tests A and C are carried out.*

A. *Melting point*, 125° to 128°, Appendix V A, Method I.

B. Dissolve 10 mg in *methanol* and dilute to 100 ml with the same solvent. Dilute 1 ml of the solution to 10 ml with *methanol*. Examined between 220 nm and 350 nm, Appendix II B, the solution shows an absorption maximum at 310 nm. The *specific absorbance* at the maximum is 340 to 360.

C. Examine by *infrared absorption spectrophotometry*, Appendix II A. The absorption maxima in the spectrum obtained with the substance being examined correspond in position and relative intensity to those in the spectrum obtained with *tinidazole EPCRS*. Examine the substances prepared as discs.

D. Examine the chromatograms obtained in the test for Related substances. The principal spot in the chromatogram obtained with solution (2) is similar in position and size to the principal spot in the chromatogram obtained with solution (3).

E. To about 10 mg add about 10 mg of *zinc powder*, 0.3 ml of *hydrochloric acid* and 1 ml of *water*. Heat in a water bath for 5 minutes and cool. The solution yields the reaction characteristic of *primary aromatic amines*, Appendix VI.

Appearance of solution Dissolve 1.0 g in *acetone* and dilute to 20 ml with the same solvent. The solution is *clear*, Appendix IV A, and not more intensely coloured than *reference solution* Y_5, Appendix IV B, Method II.

Related substances Examine by *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance.

Solution (1) Dissolve 0.20 g of the substance being examined in *methanol* with the aid of ultrasound and dilute to 10 ml with the same solvent.

Solution (2) Dilute 1 ml of solution (1) to 10 ml with *methanol*.

Solution (3) Dissolve 20 mg of *tinidazole EPCRS* in *methanol* and dilute to 10 ml with the same solvent.

Solution (4) Dilute 1 ml of solution (2) to 20 ml with *methanol*.

Solution (5) Dilute 4 ml of solution (4) to 10 ml with *methanol*.

Solution (6) Dissolve 10 mg of *2-methyl-5-nitroimidazole* (tinidazole impurity A) in *methanol* and dilute to 100 ml with the same solvent.

Solution (7) Dissolve 10 mg of *tinidazole impurity B EPCRS* in *methanol* and dilute to 100 ml with the same solvent.

Heat the plate at 110° for 1 hour and allow to cool.

Apply separately to the plate 10 µl of each solution. Develop over a path of 15 cm using a mixture of 25 volumes of *butan-1-ol* and 75 volumes of *ethyl acetate*. Allow the plate to dry in air and examine in *ultraviolet light (254 nm)*.

Any spots corresponding to tinidazole impurity A and to tinidazole impurity B in the chromatogram obtained with solution (1) are not more intense than the corresponding spots in the chromatogram obtained with solutions (6) and (7), respectively (0.5%).

Any other *secondary spot* in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (4) (0.5%) and at most one such spot is more intense than the spot in the chromatogram obtained with solution (5) (0.2%).

Heavy metals 1.0 g complies with *limit test D for heavy metals*, Appendix VII (20 ppm). Prepare the standard using 2 ml of *lead standard solution (10 ppm Pb)*.

Loss on drying Not more than 0.5%, determined on 1 g by drying in an oven at 100° to 105°, Appendix IX D.

Sulphated ash Not more than 0.1% determined on 1 g, Appendix IX A, Method II.

Assay Dissolve 0.15 g in 25 ml of *anhydrous acetic acid*. Titrate with 0.1M *perchloric acid VS*, determining the end point potentiometrically, Appendix VIII B. Each ml of 0.1M *perchloric acid VS* is equivalent to 24.73 mg of $C_8H_{13}N_3O_4S$.

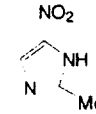
Storage Store in a well-closed container, protected from light.

Action and use Antiprotozoan; antibacterial.

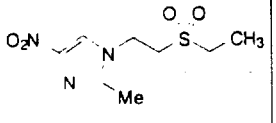
1/96

The impurities limited by the requirements of this monograph include:

2-methyl-5-nitro-1*H*-imidazole *(tinidazole impurity A)*



1-(2-ethylsulphonylethyl)-2-methyl-4-nitroimidazole *(tinidazole impurity B)*



suramin had differing toxicity. Storage in the tropics probably also affected the potency.— E. Nnochiri, *Trans. R. Soc. trop. Med. Hyg.*, 1964, *58*, 413.

Adverse Effects. Suramin may cause nausea, vomiting, abdominal pain, diarrhoea, urticaria, collapse, paraesthesia, hyperaesthesia of the hands and soles of the feet, peripheral neuritis, fever, skin rash, dermatitis, photophobia, lachrymation, amblyopia, and uveitis. A serious effect is albuminuria, with the passage of casts and blood cells. Agranulocytosis and haemolytic anaemia are rare.

When used in onchocerciasis some of the effects may represent an allergic reaction to the killed filariae.

References: Second Report of a WHO Expert Committee on Onchocerciasis, *Tech. Rep. Ser. Wld Hlth Org. No. 335*, 1966.

Pregnancy and the neonate. Suramin had teratogenic effects in *mice*.— H. Tuchmann-Duplessis and L. Mercier-Parot, *C.r. Séanc. Soc. Biol.*, 1973, *167*, 1717, per *Trop. Dis. Bull.*, 1974, *71*, 1107. A woman with advanced trypanosomiasis was successfully treated with suramin and melarsoprol, in addition to supportive therapy, from the 20th week of pregnancy; she gave birth to an apparently normal child.— M. N. Lowenthal, *Med. J. Zambia*, 1971, *5*, 175, per *Trop. Dis. Bull.*, 1972, *69*, 495.

Precautions. It should not be used in the presence of renal disease or adrenal insufficiency.

Absorption and Fate. Following intravenous injection, suramin becomes bound to plasma proteins and a low concentration in plasma is maintained for up to 3 months.

Uses. Suramin is used in the treatment of the early stages of African trypanosomiasis, especially *Trypanosoma rhodesiense* infections, but as it does not reach the cerebrospinal fluid it is ineffective in the advanced disease when the central nervous system is affected.

Suramin is administered by intravenous injection. To test the patient's tolerance, it is advisable to begin treatment with an injection of 200 mg followed, if well tolerated after 24 to 48 hours by a dose of 20 mg per kg body-weight (up to 1 g) on days 1, 3, 8, 15, and 22. The urine should be tested before each dose, and if protein is present the dose should be reduced or administration delayed.

Combined therapy with tryparsamide has been used, particularly for late *T. gambiense* infection; 12 injections can be given intravenously at intervals of 5 days, each containing suramin up to 10 mg per kg body-weight (max. of 500 mg) and tryparsamide up to 30 mg per kg (max. of 1.5 g), as a 20% solution prepared immediately before use. Two or 3 such courses have been given at intervals of 1 month. Suramin is more commonly used in conjunction with melarsoprol.

Suramin has also been used in the prophylaxis of trypanosomiasis, in a dose of 1 g to provide protection for up to 3 months, but it may mask latent infections. As with pentamidine, it is important to detect more advanced infections and to treat these with melarsoprol.

Suramin is also effective in clearing the adult filariae of onchocerciasis but has only a limited action on microfilariae. The usual dose is 1 g (after an initial test dose) weekly for 5 or 6 weeks. Diethylcarbamazine is active on the microfilariae and the 2 drugs are sometimes used in conjunction.

Onchocerciasis. Less ocular deterioration was observed in a group of patients with onchocerciasis who had been treated 14 to 15 years earlier with a single full course of suramin 4.2 g, than was seen in a similar untreated group.— F. H. Budden, *Trans. R. Soc. trop. Med. Hyg.*, 1976, *70*, 484. The incidence of optic atrophy increased from 1 in 25 to 5 in 25 three years after patients had been treated with suramin 5.2 g (total dose) for ocular onchocerciasis. There was no change in the incidence (1 in 23) in 23 patients not given suramin.— B. Taylefors and A. Rolland, *Bull. Wld Hlth Org.*, 1979, *57*, 479.

Brief discussions of the treatment of onchocerciasis.— *Br. J. Ophthal.*, 1978, *62*, 427; B. Thylefors, *Bull. Wld Hlth Org.*, 1978, *56*, 63.

Further references: B. O. L. Duke *et al.*, *Tropenmed. Parasit.*, 1976, *27*, 133; J. Anderson *et al.*, *Tropenmed. Parasit.*, 1976, *27*, 263; J. Anderson *et al.*, *Tropenmed. Parasit.*, 1976, *27*, 279.

Trypanosomiasis. See Report of a Joint WHO Expert Committee and FAO Expert Consultation, *Tech. Rep. Ser. Wld Hlth Org. No. 635*, 1979.

Preparations

Suramin Injection *(B.P.C. 1973)*. A sterile solution of suramin in Water for Injections, prepared by dissolving, immediately before use, the sterile contents of a sealed container in the requisite amount of Water for Injections. Store the sealed container in a cool place. Protect from light.

Proprietary Names

Germanin *(Bayer, Ger.)*; Moranyl *(Specia, Fr.)*.

4798-p

Teclozan. Win 13,146. *NN'-p*-Phenylenedimethylenebis[2,2-dichloro-*N*-(2-ethoxyethyl)acetamide].

$C_{20}H_{28}Cl_4N_2O_4 = 502.3$.

CAS — 5560-78-1.

White crystals. M.p. about 142°. Slightly soluble in water.

Adverse Effects. Headache, nausea, vomiting, diarrhoea, and constipation have been reported, but teclozan is generally well tolerated.

Uses. Teclozan is used in the treatment of intestinal amoebiasis. About 20% of a dose is stated to be absorbed and to be rapidly excreted. The usual dose is 100 mg thrice daily for 5 days, or 500 mg daily, in divided doses, for 3 days.

Of 51 patients with chronic intestinal amoebiasis given teclozan 750 mg daily in divided doses after meals for 2 days, 43 were reported to be cured; a further 5 patients responded to a second course of treatment with teclozan. The drug was well tolerated.— D. Huggins, *Anais Esc. nac. Saúde públ. Med. trop.*, 1971, *5*, 29, per *Trop. Dis. Bull.*, 1972, *69*, 399.

Of 30 patients with mild amoebiasis, 25 were reported cured after receiving teclozan 100 mg thrice daily for 5 days; 2 patients required a second course of treatment and 3 remained resistant to teclozan. Two patients developed diarrhoea during treatment which was otherwise well tolerated.— A. Arcilla-Latonio *et al.*, *J. Philipp. med. Ass.*, 1972, *48*, 137, per *Trop. Dis. Bull.*, 1973, *70*, 345.

A cure-rate of 92.8% (at 4 weeks) was achieved in 28 boys with chronic amoebiasis given teclozan 100 mg thrice daily for 5 days.— A. Z. El-Abdin *et al.*, *J. Egypt. med. Ass.*, 1973, *56*, 174, per *Trop. Dis. Bull.*, 1974, *71*, 1028.

Cure in 56 of 60 patients with intestinal amoebiasis after treatment with teclozan 1.5 g in 3 divided doses in 24 hours.— P. Fernandes *et al.*, *Folha med.*, 1974, *69*, 293.

Cure in 26 of 27 children, aged 1 to 5 years, with amoebiasis (usually chronic) after treatment with teclozan 750 mg in 3 divided doses in 24 hours.— H. F. Bezerra *et al.*, *Revta bras. Med.*, 1977, *34*, Suppl. (Aug.), 50.

Proprietary Names

Falmonox *(Winthrop, Arg.; Winthrop, USA)*.

4799-s

Tinidazole. CP 12574. 1-[2-(Ethylsulphonyl)ethyl]-2-methyl-5-nitroimidazole.

$C_8H_{13}N_3O_4S = 247.3$.

CAS — 19387-91-8.

Colourless crystals. M.p. about 127°.

Adverse Effects and Precautions. As for Metronidazole, p.968.

Absorption and Fate. Tinidazole is absorbed from the gastro-intestinal tract.

Pharmacokinetics of tinidazole and metronidazole in man and in *mice*.— J. A. Taylor *et al.*, *Antimicrob. Ag. Chemother.*, 1969, 267.

The biological half-life of tinidazole was 12.7 hours after administration of 150 mg as a single dose and when administered twice daily for 7 days to 7 volunteers. The maximum serum concentration was 8.91 μg per ml.— P. G. Welling and A. M. Monro, *Arzneimittel-Forsch.*, 1972, *22*, 2128. See also B. A. Wood and A. M. Monro, *Br. J. vener. Dis.*, 1975, *51*, 51, per *Abstr. Hyg.*, 1975, *50*, 382.

The peak serum concentrations of tinidazole in 4 volunteers 6 to 11 hours after a single dose of 2 g were between 20 and 40 μg per ml, and 48 hours after ingestion the serum concentration was still above the minimal trichomonacidal concentration for most of the 8 strains of *Trichomonas vaginalis* examined.— A. Forsgren and J. Wallin, *Br. J. vener. Dis.*, 1974, *50*, 146 and 148, per *Abstr. Hyg.*, 1974, *49*, 593.

In 6 gynaecological patients given a single dose of tinidazole 2 g peak serum concentrations were 32 to 52 μg per ml 3 to 6 hours after the dose, and 18 to 35 μg per ml 8.5 to 15 hours after the dose. Concentrations in saliva, vaginal secretions, peritoneal fluid, and various tissue homogenates were broadly comparable with those in serum. The plasma half-life was about 13 hours.— T. Ripa *et al.*, *Chemotherapy, Basle*, 1977, *23*, 227, per *Int. pharm. Abstr.*, 1977, *14*, 1084.

In 4 healthy subjects given tinidazole 2 g concentrations in the CSF 90 minutes later (17 to 39 μg per ml) were 88% of those in serum.— A. M. M. Jokipii *et al.*, *J. antimicrob. Chemother.*, 1977, *3*, 239.

Uses. Tinidazole which is a nitroimidazole like metronidazole has antiprotozoal activity and is effective against *Trichomonas vaginalis*, *Entamoeba histolytica*, and *Giardia lamblia*. It is also active against anaerobic bacteria.

In trichomoniasis it is given by mouth in a dose of 150 mg twice daily for 7 days or as a single dose of 2 g to both men and women. It has been given in similar doses in the treatment of giardiasis.

In amoebiasis doses of 2 g once daily for 3 days are commonly used.

A review of tinidazole in the treatment of trichomoniasis, amoebiasis, and giardiasis.— P. R. Sawyer *et al.*, *Drugs*, 1976, *11*, 423.

Proceedings of a symposium on the use of tinidazole in the treatment of amoebiasis, giardiasis, and trichomoniasis.— *Drugs*, 1978, *15*, *Suppl.* 1, 1–60.

The following anaerobic bacteria were inhibited by 3.1 μg per ml of tinidazole and killed by 6.3 μg per ml: *Bacteroides fragilis* and *melaninogenicus*, *Clostridium perfringens* and other species of clostridia, *Eubacterium*, *Fusobacterium*, *Peptococcus*, *Peptostreptococcus*, and *Veillonella* spp. *Propionibacterium acnes* was relatively resistant. The same figures were achieved with metronidazole and ornidazole.— J. Wüst, *Antimicrob. Ag. Chemother.*, 1977, *11*, 631.

The median minimum inhibitory concentration of tinidazole against *Bacteroides* spp. was 0.12 μg per ml compared with 0.25 μg per ml for metronidazole or nimorazole.— R. Wise *et al.*, *Chemotherapy, Basle*, 1977, *23*, 19.

The activities of clindamycin, tinidazole, and doxycycline *in vitro* were compared against 376 anaerobic bacteria. Clindamycin and tinidazole had MICs of 0.5 and 3 μg per ml respectively against 90% of 200 strains of *Bacteroides fragilis*. Tinidazole had an MIC of 12 μg per ml against 72 strains of the *Clostridium* spp. but benzylpenicillin and ampicillin were more active. Tinidazole was generally less active than benzylpenicillin, ampicillin, cephalothin, carbenicillin, erythromycin, chloramphenicol, tetracycline, and doxycycline against 20 strains of *Bacteroides melaninogenicus*, 54 of the *Fusobacterium* spp., and 30 strains of anaerobic Gram-positive cocci.— J. Klastersky *et al.*, *Antimicrob. Ag. Chemother.*, 1977, *12*, 563.

Amoebiasis. In a series of controlled studies 436 patients with intestinal amoebiasis were treated with tinidazole 600 mg twice daily for 5 days or 2 g once daily for 3 days, or metronidazole 400 mg thrice daily for 5 days or 2 g once daily for 3 days. Cure-rates for tinidazole were 97.2% and 88.3% respectively in patients passing trophozoites and 81.2% and 93.4% in those passing cysts, compared with 87.5% and 73.3%, and 84.2% and 47.3% for metronidazole. A cure-rate of 96% was achieved in 50 patients with hepatic amoebiasis given tinidazole 2 g once daily for 2 days, compared with 75.5% in 49 given metronidazole. A cure-rate of 88.3% was achieved in 94 patients with giardiasis given tinidazole in a mean dose of 61.8 mg per kg as a single dose, compared with 46.7% in 92 given metronidazole 56 mg per kg.— J. S. Bakshi *et al.*, *Drugs*, 1978, *15*, *Suppl.* 1, 33.

In a multicentre study in 8 countries a cure-rate of 95% was achieved in 502 patients with amoebiasis given tinidazole 2 g once daily (50 mg per kg body-weight for children) for 2 or 3 days. An excellent response was achieved in 60, and a good response in 17, of 82 with hepatic amoebiasis. A cure-rate of 88% was achieved in 24 children with giardiasis given a single dose of about 50 mg per kg. A cure-rate of 95.2% was achieved in 859 patients with trichomonal vaginitis given a single dose of 2 g.— V. V. Apte and R. S. Packard, *Drugs*, 1978, *15*, *Suppl.* 1, 43.

Of 88 aboriginal children infected with *Giardia lamblia* or *Entamoeba histolytica* 23 received a single dose of tinidazole 1 to 1.5 g, 23 tinidazole 1 to 1.5 g daily for 3 days, 23 metronidazole 200 mg twice daily for 5 days, and 19 were left untreated. Both metronidazole and tinidazole successfully cleared the majority of *G. lamblia* infections but *E. histolytica* infections were more effectively treated with tinidazole. A single dose of tinidazole was as effective as the longer regimen. No adverse reactions occurred with either drug.— J. S. Welch *et al.*, *Med. J. Aust.*, 1978, *1*, 469.

Further references: N. Islam and M. Hasan, *Curr. ther. Res.*, 1975, *17*, 161; J. N. Scragg *et al.*, *Archs Dis. Childh.*, 1976, *51*, 385.

Liver abscess. Tinidazole 57 mg per kg body-weight daily for 5 days or 50 mg per kg daily for 3 days was effective in the treatment of amoebic liver abscess in 23 of 25 children aged 3 months to 6 years.— J. N. Scragg and E. M. Proctor, *Archs Dis. Childh.*, 1977, *52*, 408.

Of 16 patients with hepatic amoebiasis 15 were cured after treatment with tinidazole 2 g as a single dose daily for 3 to 6 days, compared with 12 of 15 given metronidazole in the same dosage regimen for 4 to 10 days.— N. Islam and K. Hasan, *Drugs*, 1978, *15*, *Suppl.* 1, 26.

Further references.— H. A. Meyer, *E. Afr. med. J.*, 1974, *51*, 923, per *Trop. Dis. Bull.*, 1975, *72*, 720; S. N. Mathur *et al.*, *J. int. med. Res.*, 1977, *5*, 429; M. A. Quaderi *et al.*, *J. trop. Med. Hyg.*, 1978, *81*, 16.

Giardiasis. Cure in 35 of 38 children with giardiasis after a single dose of tinidazole; 2 others were cured after a second dose. Doses were: under 1 year, 500 mg; 7 years, 1 g; 12 years, 1.5 g.— S. Danzig and W. L. F. Hatchuel (letter), *S. Afr. med. J.*, 1977, *52*, 708, per *Trop. Dis. Bull.*, 1978, *75*, 783.

A cure-rate of 96.7% in patients with giardiasis treated with tinidazole 150 mg twice daily for 7 days.— G. C. Levi *et al.*, *Am. J. trop. Med. Hyg.*, 1977, *26*, 564, per *Trop. Dis. Bull.*, 1978, *75*, 648. See also S. Y. Salih and R. E. Abdalla, *J. trop. Med. Hyg.*, 1977, *80*, 11, per *Trop. Dis. Bull.*, 1977, *74*, 731.

Cure of 53 of 55 patients with giardiasis given tinidazole 2 g as a single dose.— N. A. El Masry *et al.*, *Am. J. trop. Med. Hyg.*, 1978, *27*, 201, per *Trop. Dis. Bull.*, 1978, *75*, 544.

See also under Amoebiasis, above.

Further references: L. Jokipii and A. M. M. Jokipii, *J. infect. Dis.*, 1979, *140*, 984; M. B. Tadros, *J. Egypt. Soc. Parasit.*, 1979, *9*, 467, per *Trop. Dis. Bull.*, 1980, *77*, 125; A. Sabchareon *et al.*, *S.E. Asian J. trop. med. publ. Hlth*, 1980, *11*, 280, per *Trop. Dis. Bull.*, 1981, *78*, 161.

Prophylaxis in surgery. In a prospective, randomised, double-blind study of 6 months' duration involving 71 patients 2 g of tinidazole given before surgery prevented wound infection after elective colonic surgery in 37 of 40 patients in comparison with 28 of 31 patients treated with placebo.— P. S. Hunt *et al.*, *Med. J. Aust.*, 1979, *1*, 107.

Postoperative infections occurred in 6 of 50 patients who received 2 g of tinidazole 12 to 18 hours before undergoing elective abdominal hysterectomy and 2 g 48 hours postoperatively; infections occurred in 28 of 50 similar control patients.— P. C. Appelbaum *et al.*, *Chemotherapy, Basle*, 1980, *26*, 145.

Further references: J. Adno and R. Cassel, *S. Afr. med. J.*, 1979, *56*, 565 (gynaecological surgery); M. Karhunen *et al.*, *Br. J. Obstet. Gynaec.*, 1980, *87*, 70 (hysterectomy).

Trichomoniasis. Tinidazole 2 g as a single dose produced parasitological cure in 47 of 50 patients with trichomoniasis, compared with 32 of 50 given metronidazole.— R. Anjaneyulu *et al.*, *J. int. med. Res.*, 1977, *5*, 438.

Further reports of the successful use of 2-g doses of tinidazole in women.— H. T. M. Rao and D. R. Shenoy, *J. int. med. Res.*, 1978, *6*, 46; J. P. Ward, *Med. J. Aust.*, 1976, *2*, 651; R. Jones and P. Enders, *ibid.*, 1977, *2*, 679; M. Massa *et al.*, *Boln chil. Parasit.*, 1976, *31*, 46, per *Trop. Dis. Bull.*, 1977, *74*, 291.

Successful use in men of single 1-g doses of tinidazole.— N. Kawamura, *Br. J. vener. Dis.*, 1978, *54*, 81, per *Abstr. Hyg.*, 1978, *53*, 465.

See also under Amoebiasis, above.

Vaginitis. Administration of a single dose of tinidazole 2 g to 35 women with *Gardnerella vaginalis (Haemophilus vaginalis)* infection led to disappearance of the bacteria in 33; of the other 2 women the count was reduced in one and a repeat treatment was successful in the second. Two women relapsed after 15 to 20 days and repeat treatment was successful. All the patients' partners were given the same dose of tinidazole, and abstinence from sexual intercourse was recommended for at least 24 hours.— M. Bardi *et al.* (letter), *Lancet*, 1980, *1*, 1029.

See also under Trichomoniasis, above.

Proprietary Names

Fasigin *(Pfizer, Ital.)*; Fasigyn *(Pfizer, Arg.; Pfizer, Austral.; Roerig, Belg.; Pfizer, Denm.; Pfizer, Neth.; Pfizer, Norw.; Pfizer, S.Afr.; Pfizer, Swed.; Pfizer, Switz.)*; Fasigyne *(Pfizer, Fr.)*; Simplotan *(Pfizer, Ger.)*; Trichogin *(Chiesi, Ital.)*; Tricolam *(Pfizer, Spain)*.

6000-c

Tryparsamide *(B.P. 1968)*. Tryparsam.; Tryparsamidum; Glyphenarsine; Tryparsone. Sodium hydrogen 4-(carbamoylmethylamino)phenylarsonate hemihydrate. $C_8H_{10}AsN_2NaO_4.\frac{1}{2}H_2O = 305.1$.

CAS — 554-72-3 (anhydrous); 6159-29-1 (hemihydrate).

Pharmacopoeias. In *Ind.*, *Int.*, *It.*, *Mex.*, and *Turk.*

A colourless, odourless, crystalline powder which is slowly affected by light.

Soluble 1 in 1.5 of water, forming a neutral solution; soluble 1 in 3500 of alcohol; practically insoluble in chloroform and ether. A 4.62% solution is iso-osmotic with serum. Aqueous solutions deteriorate on storage and should be used immediately after preparation; solutions for injection are prepared aseptically. Store in a cool place in small airtight containers. Protect from light.

Adverse Effects. Side-effects include dizziness, tinnitus, nausea, vomiting, headache, fever, exfoliative dermatitis, allergic reactions, and bradycardia immediately after an injection. Liver damage may also occur.

The most serious toxic effect is upon the optic nerve. Treatment should be discontinued immediately if visual defects appear; though blindness may occur suddenly, especially if optic injury is already present, visual defects may not become apparent until a few weeks after a course of treatment has been completed.

Uses. Tryparsamide is trypanocidal. Because it penetrates the cerebrospinal fluid it has been used in the treatment of African trypanosomiasis with central nervous system involvement particularly in *Trypanosoma gambiense* infections. It has been given in doses of 30 to 60 mg per kg body-weight (up to maximum of 2 g) intravenously each week for 12 to 14 weeks. The trypanosomes may become resistant to tryparsamide. Because of the risk of blindness, melarsoprol is now preferred.

For the use of tryparsamide in conjunction with suramin, see p.984.

Preparations

Tryparsamide Injection *(B.P. 1968)*. Tryparsam. Inj. A sterile solution in Water for Injections, prepared by dissolving, immediately before use, the sterile contents of a sealed container in the requisite amount of Water for Injections.

Database: Medline <1995 to February 1998>

<1>
Unique Identifier
96415043
Authors
Salo JP. Salomies H.
Title
High performance thin layer chromatographic analysis of hydrolyzed tinidazole solutions. II. Hydrolysis kinetics of tinidazole.
Source
Journal of Pharmaceutical & Biomedical Analysis. 14(8-10):1267-70, 1996 Jun.
Abstract
In a citrate-borate-phosphate buffer, 5 mM tinidazole solutions exhibited maximum stability stability around pH 4.0-5.0. The hydrolysis of tinidazole was mostly a first-order reaction. At pH 10.0 and 60-80 degrees C, tinidazole had an activation energy of 122 kJ mol-1 for hydrolysis. It was postulated that tinidazole decomposes by different mechanisms under basic and neutral/acidic conditions.

<2>
Unique Identifier
96415042
Authors
Salo JP. Salomies H.
Title
High performance thin layer chromatographic analysis of hydrolyzed tinidazole solutions. I. Development and validation method.
Source
Journal of Pharmaceutical & Biomedical Analysis. 14(8-10):1261-6, 1996 Jun.
Abstract
A stability-indicating high performance thin layer chromatography method for analyzing hydrolyzed tinidazole solutions using silica gel plates was developed and validated. The mobile phase used was methanol-diethyl ether-chloroform (1:9:3, v/v/v) allowing small changes in its composition. Detection was at 314 mm. Rf values being 0.1-0.4, baseline resolution was achieved for tinidazole and the hydrolysis products. The analytes were stable on the sorbent and could be precisely and accurately measured

in the range 20-170 ng per band.

TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE, VOL. 77, NO. 6, 845-846 (1983)

Treatment of non-invasive amoebiasis. A comparison between tinidazole alone and in combination with diloxanide furoate

PEHROLOV PEHRSON AND ELIAS BENGTSSON

Dept. of Infectious Diseases, Karolinska Institute, Roslagstull Hospital, Box 5651, S-114 89 Stockholm, Sweden

Summary

Tinidazole (40 mg/kg body-weight in one daily dose for five days) and tinidazole (same dose) plus diloxanide furoate (20 mg/kg body-weight divided into three daily doses for 10 days) were compared as treatments for amoebiasis. The parasitic cure rates were 44 and 91% respectively. We cannot, therefore, recommend tinidazole alone in this dosage as a treatment for non-invasive amoebiasis.

Introduction

Tinidazole (Fasigyn) has recently been widely used as an alternative to metronidazole for the treatment of infections with *Entamoeba histolytica*. In a previous study (PEHRSON, 1982), tinidazole was given to a series of patients with chronic intestinal or asymptomatic amoebiasis. When checked by at least three stool specimens taken on different days, one month after treatment, we found a parasitic cure rate (p.c.r.) of 0% (0/14). This should be compared with the results obtained in other studies, showing a cure rate of 77 to 96% (MISRA & LAIQ, 1974; PRAKASH *et al.*, 1974; JOSHI & SHAH, 1975; BAKSHI *et al.*, 1978), using the same dosage schedule but mainly in cases of acute intestinal amoebiasis.

To investigate the reasons for the unsatisfactory response we obtained, which could be due to too low a dose or to a low efficiency of tinidazole in the gut lumen, we carried out a new trial with a higher daily dose of tinidazole and compared the effect of this higher dose with that following treatment with tinidazole and diloxanide furoate (Furamide) in combination. This latter was found to be an effective intraluminal amoebicide (WOODRUFF & BELL, 1960, 1967; WOLFE, 1973), whose mode of action upon the amoeba is unknown. We omitted Furamide as a single regimen, because it is considered to be ineffective against invasive amoebiasis and there is always a risk of developing an invasive form of the disease if zymodeme differentiation of strains of *Entamoeba histolytica* is not performed routinely (SARGEAUNT & WILLIAMS, 1978; SARGEAUNT *et al.*, 1982).

Materials and Methods

During the period of the study, 41 patients were diagnosed as suffering from amoebiasis. All of them were supposed to have contracted their infections abroad, as amoebiasis is not considered to be endemic in Sweden. No cases of acute, dysenteric amoebiasis or diagnosed or suspected cases of liver abscess were included. The patients had not received any anti-amoebic drug during the previous year. Nine of the patients had a concomitant infection with *Giardia lamblia*, two with *Shigella flexneri*, two with *Campylobacter jejuni*, one with *Salmonella paratyphi A*, one with *Hymenolepis nana*, one with *Ascaris lumbricoides* and one with *Trichuris trichiura*.

In a predetermined, random order, the patients were allocated to two groups, 18 being treated with tinidazole alone and 23 with the combination. All were hospital in-patients and kept under supervision during treatment.

Dosage schedules

(1) tinidazole 40 mg/kg body-weight in one daily dose for five days;

(2) tinidazole as above plus diloxanide furoate 20 mg/kg body-weight divided into three daily doses for 10 days.

Approximately one month after the treatment was completed, checks were made, including the examination of at least three stool specimens taken on different days. One of these was examined by direct microscopy of freshly passed, loose faeces induced by a 50% magnesium sulphate purgative and the other normally passed specimens were examined by the formol-ether-concentration technique described by RIDLEY & HAWGOOD (1956). Failure was defined as the persistence of amoebic trophozoites or cysts in any of these specimens.

Those in whom the treatment with tinidazole failed were later treated with the combination of tinidazole and diloxanide furoate and those in whom the combination failed were treated with metronidazole 40 mg/kg body-weight daily for 10 days.

Results

Data on the participants and the results of the checks one month after treatment are shown in Table I. In no case were the side effects severe enought to cause cessation of treatment. Statistical analysis was made, using the chi-square test, and showed a significant difference between the two groups on the 1%-level (two-tailed test) and in favour of the combination. No differences could be found between the response of Swedes and that of the immigrants, or between those infected on different continents (Asia, Africa, South America). The presence of other parasites did not seem to affect the outcome of the treatment.

Discussion

Our results with tinidazole alone (44% p.c.r.), in treating non-dysenteric amoebiasis, are unsatisfactory and differ very much from those obtained in previously published studies by different authors, using the same dosage schedules (77 to 96% p.c.r.) (ISLAM & HASAN, 1975; APTE & PACKARD, 1978) or lower (MISRA & LAIQ, 1974; PRAKASH *et al.*, 1974; JOSHI & SHAH, 1975; BAKASHI *et al.*, 1978). The patients in these studies were, however, mainly cases of acute amoebic dysentery, a factor which may have influenced the results.

A weak amoebicidal effect of the nitroimidazoles on the cyst stage of *E. histolytica* was observed by

Table I—Some characteristics and treatment results of 41 patients with non-invasive amoebiasis

Treatment	No.	Median age (age range) years	Patients with symptoms v. asymptomatics	Swedes v. other nationalities	Parasite-free at check	Parasite cure rate
Tinidazole 40 mg/kg × 1 + V	18	28 (9-68)	11:7	8:10	8	44%
Tinidazole 40 mg/kg × 1 × V + diloxanide furoate 500 mg × 3 × X	23	26 (6-68)	15:8	11:12	21	92%

SPILLMAN *et al.* (1976), but this report was contradicted by BAKSHI *et al.* (1978). Our drug trial was carried out in a country in which amoebiasis is not endemic, making reinfection during follow-up very unlikely, and confirming that the low p.c.r. was caused by "true" treatment failures.

We therefore believe that our poor results with tinidazole alone are due to its ineffectiveness in eradicating cysts in the lumen of the gut, either because of too effective absorption (MONRO, 1974) or inactivation by aerobic organisms as shown by RALPH & CLARKE (1978).

When tinidazole was combined with diloxanide furoate, we obtained a cure rate of 91%, which may be compared with studies by WOODRUFF & BELL (1967), in which they reported a cure rate of 95% in amoebic cyst-passers treated with diloxanide furoate alone for 10 days and WOLFE (1973), who found a cure rate of 83% using the same schedule. It is also noteworthy that all our failures with tinidazole alone have proved to be freed from their infection after treatment with the combination.

Acknowledgements

We wish to thank Mrs. Inger Pontén, the head nurse in the tropical ward and Birgit Lindberg, the chief technician at the laboratory of tropical diseases, for their devoted work with the patients.

References

Apte, V. V. & Packard, R. S. (1978). Tinidazole in the treatment of trichomoniasis, giardiasis and amoebiasis. Report of a multicentre study. *Drugs*, **15** (Suppl. 1), 43-48.

Bakshi, J. S., Ghiara, J. M. & Nanivadekar, A. S. (1978). How does Tinidazole compare with Metronidazole? A summary report of Indian trials in amoebiasis and giardiasis. *Drugs*, **15** (Suppl. 1), 33-42.

Islam, N. & Hasan, M. (1975). Tinidazole in the treatment of intestinal amoebiasis. *Current Therapeutic Research*, **17**, 161-165.

Joshi, H. D. & Shah, B. M. (1975). A comparative study of tinidazole and metronidazole in treatment of amoebiasis. *Indian Practitioner*, **28**, 295-302.

Misra, N. P. & Laiq, S. M. (1974). Comparative trial of tinidazole and metronidazole in intestinal amoebiasis. *Current Therapeutic Research*, **16**, 1255-1263.

Monro, A. H. (1974). Blood levels of chemotherapeutic drugs and the pharmacokinetics of tinidazole and metronidazole. *Current Medical Research and Opinion*, **2**, 130-136.

Pehrson, P. O. (1982). The treatment of non-invasive amoebiasis—a comparison between metronidazole and tinidazole. *Annals of Tropical Medicine and Parasitology*.

Prakash, C., Bansal, B. C. & Bansal, M. R. (1974). Tinidazole in symptomatic intestinal amoebiasis. *Journal of Tropical Medicine and Hygiene*, **77**, 165-167.

Ralph, E. D. & Clark, D. A. (1978). Inactivation of metronidazole by anaerobic and aerobic bacteria. *Antimicrobial Agents and Chemotherapy*, **14**, 377-383.

Ridley, D. S. & Hawgood, B. C. (1956). The value of formol-ether concentration of faecal cysts and ova. *Journal of Clinical Pathology*, **9**, 74-76.

Sargeaunt, P. G. & Williams, J. E. (1978). The differentiation of invasive and non-invasive *Entamoeba histolytica* by isoenzyme electrophoresis. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **72**, 519-521.

Sargeaunt, P. G., Jackson, T. F. H. G. & Simjee, A. (1982). Biochemical homogeneity of *Entamoeba histolytica* isolates, especially those from liver abscess. *Lancet*, **i**, 1386-1388.

Spillman, R., Ayala, S. C. & de Sanchez, C. E. (1976). Double blind test of metronidazole and tinidazole in the treatment of asymptomatic *Entamoeba histolytica* and *Entamoeba hartmanni* carriers. *American Journal of Tropical Medicine and Hygiene*, **25**, 549-551.

Wolfe, M. S. (1973). Nondysenteric intestinal amoebiasis. Treatment with diloxanide furoate. *Journal of the American Medical Association*, **244**, 1601-1604.

Woodruff, A. W. & Bell, S. (1960). Clinical trials with entamide furoate and related compounds: I In a non-tropical environment. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **54**, 389-395.

Woodruff, A. W. & Bell, S. (1967). The evaluation of amoebicidies. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **61**, 435-439.

Accepted for publication 30th March, 1983.